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A REVIEW OF THE DIETETIC FACTORS IN LIVER DISEASE

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I.—DIETARY CIRRHOSIS AND NECROSIS OF THE LIVER*

Two distinct disorders of the liver have been produced in animals by defective diets. The first is a fatty infiltration of the liver which proceeds slowly to cirrhosis of the portal type. The second is acute necrosis, which, if not fatal, is followed by post-necrotic scarring and nodular hyperplasia. The two lesions may sometimes commingle, and not all workers would agree that they can be sharply differentiated.

Fatty Infiltration and Cirrhosis of the Liver

Soon after insulin was discovered it was observed that pancreatectomized dogs kept alive by diet and insulin tended to develop severe fatty infiltration and eventual cirrhosis of the liver, which could be prevented by feeding them with pancreas. Experiments showed that lecithin also was effective, and likewise choline, which is one of the components of lecithin. The effect of pancreas is probably not entirely explained by lecithin, for pancreas contains another substance called lipocaic, which has an action in discharging fat from the liver. Fatty infiltration and cirrhosis can also be produced in intact animals by giving a high-fat diet, and subsequent work has for convenience been done mostly on small animals such as rats and mice. The process is a slow one, but after an interval of several months a progressive fibrosis of the portal type develops, presumably because the excess of fat interferes with the nutrition of the liver cells. It can be checked at any time by lecithin or choline, which bring the fat content of the liver back to normal. The maintenance dose of choline is probably of the order of 1 mg. per 100 g. body weight of rat per day, though it is customary to give ten or twenty times this amount, and high dosage is necessary for curative purposes.

Later it was found that the addition of adequate amounts of casein to the diet prevented fatty infiltration, and it was a natural step from this to discover that fatty infiltration could be produced by reduction of the protein, even in the absence of a high fat intake. Whereas casein prevents fatty infiltration, gelatin is relatively ineffective, and the action of casein appears to be explained by one of its component amino-acids, methionine. Choline and methionine have in common the possession of methyl (CH_3) groups, which are fairly loosely attached—in the one case to nitrogen, in the other to sulphur atoms. These labile methyl groups are very important in the economy of the body. When there is a deficiency of labile methyl groups the body is unable to manufacture lecithin, which is required for the transport of fat, and the fat therefore accumulates in the liver and eventually damages it. Cystine, which resembles methionine in containing sulphur but contains no methyl groups, has no curative action in fatty infiltration, though it is effective against acute necrosis. Substances which encourage the normal transfer of fat from the liver are called lipotropic (McHenry and Patterson, 1944), and the series I have mentioned is the most important:

Pancreas→lecithin→choline→labile methyl group
Casein→methionine ⟶

Fatty infiltration of the liver in the pancreatectomized animal is probably due to the absence of an enzyme, perhaps identical with lipocaic, which liberates methionine from combination and makes it available as a lipotropic factor (Chaikoff, Entenman, and Montgomery, 1945).

Acute Necrosis of the Liver

When allowance was made for the lipotropic action which proteins share with choline owing to the possession of labile methyl groups, it was possible to show that protein deficiency may also act in a quite different and specific way and produce acute necrosis of the liver (Himsworth and Glynn, 1944a). In contrast to the gradual development of fatty engorgement and cirrhosis of the liver over a period of months, acute necrosis comes on suddenly in the midst of apparent health after an interval of several weeks on the defective diet. The time of onset and the severity of the attack depend mainly on the degree of deficiency of the diet. Different proteins vary in their ability to prevent necrosis; whereas casein is effective in small amounts, yeast protein is ineffective in large amounts. The main difference between the two proteins is that yeast is poor in amino-acids containing sulphur, and in fact the protective value of different strains of yeast has been shown to vary in proportion to their nitrogen–sulphur ratios.

The two thio-amino-acids are methionine and cystine. By feeding rats on synthetic diets in which the nitrogen was supplied in the form of pure amino-acids it has been shown that necrosis will not develop if an adequate amount of cystine is supplied (Glynn, Himsworth, and Neuberger, 1945). Cystine can be replaced by methionine, which is converted into cystine in the body. These results suggest that the essential factor in preventing dietary necrosis is the sulphydryl (SH) group, just as the methyl (CH_3) group is the essential factor in preventing dietary cirrhosis. The broken link in the metabolic chain in sulphydryl deficiency is presumably cystine, whereas the broken link in methyl deficiency is phospholipin. Methionine, which contains both methyl and sulphydryl groups, is a key substance in the metabolism of the liver, and it is one of the indispensable amino-acids. There is evidence that an excess of cystine may be harmful. Glynn and his co-workers obtained protection with 30 mg. per rat per day, whereas Earle and Victor (1942) found that 300 mg. per rat per day produced lesions which were apparently of the necrotic type. This

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last figure would correspond with a human dose of 180 g., so that ill-effects need not be feared in therapeutic experiments in man.

It should be noted that yeast does not actively favour necrosis: it is merely poorly protective. Yeast is a good source of choline, and it possibly contains other unknown lipotropic principles (György and Goldblatt, 1939; Rich and Hamilton, 1940). Yeast may therefore be expected to be a useful remedy in most forms of fatty infiltration of the liver due to dietary imbalance. Some of the B vitamins, particularly biotin, favour the deposition of fat in the rat's liver; this type of fatty liver is resistant to choline but responds to lipocaic or inositol. In fact, the relation of the B vitamins to cirrhosis and necrosis of the liver has not yet been completely elucidated. Growing rats and mice have a high rate of metabolism, which affects their vitamin B requirements, and in larger animals the action of the B vitamins on the liver may be different (Fouts, 1943). On the present evidence it seems a justifiable conclusion that no ill effects on the liver are likely to accrue from massive dosage with yeast or other sources of the vitamin B complex in hepatic disease in man.

Diet and Resistance to Hepatitis

In view of the gross damage to the liver which may result from dietary defect it is not surprising that lesser deficiencies may impair the resistance of the liver to injury by poisons. It has been known for many years that animals which have been starved or been fed on an excessive proportion of fat develop fatty infiltration of the liver, and with this goes a diminished resistance to a number of hepatic poisons. It has also long been known that a damaged liver contains little glycogen, and that animals fed on high-carbohydrate diets are in general less susceptible to drugs which produce accumulation of fat in the liver than are those given high-fat diets (Rosenfeld, 1903). Not only does a high carbohydrate intake give some protection against poisoning by chloroform and phosphorus but it is also of value in the prevention of hepatic damage following experimental ligation of the common bile-duct, operation of Eck's fistula, partial hepatectomy, and experimental mushroom poisoning (Soskin and Hyman, 1939).

For carbohydrate to be effective it is probably necessary that glycogen should be deposited in the liver, that fat should be displaced, and that the ingested carbohydrate should spare the body stores of protein. It is an unfortunate error to think that the mechanical displacement of fat by glycogen is the whole story. The truth is rather that carbohydrate is the fuel for the hepatic cell in its work of fat transport, protein synthesis, and detoxication. The great value of carbohydrate may well be that it spares protein. Carbohydrate is not entirely comparable to the petrol in the internal combustion engine, as it may be used to neutralize poisons by forming conjugates with them, but its action is mainly as a source of energy which is quickly consumed. Carbohydrates cannot protect the liver unless the requirements of protein metabolism and total calories are satisfied. If these precautions are not observed an unbalanced carbohydrate regimen may actually favour the development of necrosis (Craven, 1931).

Attention was first concentrated on the part played by protein in maintaining the resistance of the liver when Davis and Whipple (1919) demonstrated that not only carbohydrate but also protein would protect the starved dog against chloroform poisoning. Much of the subsequent work of Whipple and his group has been done with dogs depleted of protein by special diets and sometimes by withdrawal of plasma as well. They have shown that injury to the liver from chloroform increases as protein stores decrease; and that a protein meal before anaesthesia is beneficial (Miller and Whipple, 1940). They demonstrated that the sulphur-containing amino-acids, methionine and cystine, are the specific protective factors and that methionine is more effective than cystine. Finally Brunschwig and his co-workers (1945) showed that equal protection was given by the non-nitrogenous compound thioglycollate, and the only common factor was the simple sulphydryl (SH) group. While chloroform damages the liver of the normal dog, with the organic arsenicals the dog must first be depleted of protein, or the animal will die from the other toxic effects of the arsenic before the liver is attacked. Here again the protective action of protein has been demonstrated and traced to the methionine level.

There are fewer experiments on the resistance of animals with choline deficiency, presumably because it has so long been known that the fatty liver is vulnerable and also because fatty infiltration may only slowly disappear under specific treatment. Best and his co-workers (Best *et al.*, 1935; Barrett, 1939) have shown that when rats are maintained on a diet low in lipotropic factors and then poisoned with phosphorus or carbon tetrachloride the addition of choline to the diet has no effect on the degree of fatty infiltration or damage to the liver cells, but it speeds up the rate of disappearance of fat from the liver in the recovery phase.

This brings us to the time factor in protection experiments, which is of special importance when we come to apply the results to man, for in man we can rarely take action till exposure has occurred. Methionine will give complete protection against chloroform if administered shortly before anaesthesia. It will give partial protection three to four hours after anaesthesia, but no protection more than four hours after anaesthesia (Miller and Whipple, 1942). With mapharside protection has been obtained by the oral administration of methionine 20 to 24 hours before the injection of the arsenical, but only partial protection with intravenous injection just prior to mapharside injection. The latter failure may well be due to too small a dose—1 g. per dog, instead of the 3 g. used in the other experiments (Goodell *et al.*, 1944). Most of the work so far recorded has dealt with animals on defective diets. A variety of food factors, including methionine, glucose, para-amino-benzoic acid (Sandground and Hamilton, 1943), liver extract, and sodium xanthine (Barrett *et al.*, 1938), will enhance the normal resistance against certain poisons, but there is no evidence that choline can act in this way.

Dietary Treatment of Experimental Hepatitis

The lipotropic action of protein and the antinecrotic action of the protein sulphur lead us to expect that protein would be of great value in the treatment of hepatic injury, and at first sight it is puzzling to find that apparently it is not. Treatment is a different thing from prophylaxis. Much of the experimental assessment of therapy has been carried out on animals poisoned with carbon tetrachloride. Some of the factors affecting recovery from carbon tetrachloride poisoning have been carefully studied by Lamson, Minot, and Robbins (1928). They found that dogs treated with carbon tetrachloride more commonly died from acute necrosis when they were on a lean-meat diet than on a mixed diet containing bone-meal. The addition of calcium to the preceding diet of lean meat reduced the mortality to normal. Acute necrosis after carbon tetrachloride in man is more common in children and in the malnourished, and they suspect that this is due to calcium deficiency. Lamson (1930) recalled that Whipple had found that a high-carbohydrate diet protects dogs against poisoning by chloroform, and he pointed out that such a diet usually takes the form of bread-and-milk, which is high in calcium and low in meat.

The high-calcium diet does not diminish the liver damage: it merely diminishes the symptoms. These symptoms are attributed to a high blood level of guanidine, which leads to severe hypoglycaemia and peripheral circulatory failure. Calcium salts neutralize the guanidine, and glucose repairs the hypoglycaemia. On this argument death in hepatitis may be due to incomplete metabolites or products of autolysis, and if these can be neutralized spontaneous recovery may occur. Lamson (1930) further showed that the feeding of meat to susceptible animals causes a tremendous increase in blood guanidine, with a fall in blood sugar, tetany, convulsions, gastro-intestinal haemorrhage, and death. Guanidine has always been something of a will-o'-the-wisp in metabolic diseases, and this line of research has seemingly been held up by the necessity for studying its pharmacology. Certainly Bollmann and Mann (1936) found no excess of guanidine in the experiments described in the next paragraph. The relief of the symptoms of acute necrosis of the liver by calcium recalls recent work on adenosine triphosphate, which is believed to be an important factor in shock from tissue damage. Adenosine triphosphate is potentiated by magnesium, and magnesium and calcium are physiological antagonists (Green and Stoner, 1944).

Bollmann and Mann (1936) have experimented with diets in a variety of hepatic injuries in dogs. After performance of Eck's fistula a condition known as meat intoxication is liable to develop, though the name perhaps exaggerates the extent to which it is due to meat. After complete obstruction of the bile-duct a diet rich in carbohydrate becomes increasingly necessary for the maintenance of the animal. After two or three months a diet exclusively of meat will prove fatal within a week, but if the diet is high in carbohydrate life may be prolonged for at least a year. The animals are extraordinarily prone to develop ascites after feeding on meat. The active substance which induces ascites is probably not protein, because milk protein does not favour ascites, whereas meat extract produces results which are even more striking than those of meat. Comparable results were obtained with 16 dogs, each of which was given 10 ml. of carbon tetrachloride daily by mouth. The four dogs that were given a high-fat diet all died within three weeks. Of the four dogs that were given an entirely meat diet, two died within three months, and the other two had ascites. The remaining eight dogs, which were given mixed diets, were all alive at the end of three months, though the four which had received their protein in the form of meat were not in such good shape as those which had received milk.

Bollmann (1943) has more recently determined the time of survival of rats which were exposed to carbon tetrachloride vapour for 30 minutes three times a week. On the ordinary mixed diet the rats lived from 36 to 42 days. In a second group of experiments half of this diet was replaced with isocaloric values of cracker-meal and sucrose, meat, or lard. Expressing the normal survival time as 100, the investigators obtained the following figures for survival: carbohydrate, 146; protein, 100; fat, 91. In another series three-fourths of the mixed diet was replaced with isocaloric values of the above foodstuffs, and the protective values were now: carbohydrate, 205; protein, 104; fat, 59.

Dietary Cirrhosis of the Liver in Man

A low intake of protein with insufficient supply of the vitamin B complex, including choline, is a prominent feature of the diet of persons addicted to alcohol. In the earlier stages of alcoholism fatty infiltration of the liver is said to occur, and there is a growing tendency to affiliate alcoholic cirrhosis with the cirrhosis produced in animals by lack of lipotropic factors. But alcohol is not the only cause of cirrhosis in man, nor is it the commonest. All writers on tropical pathology have laid stress on the frequency of liver cirrhosis with ascites among native races, where the influence of alcohol can be discounted (Manson-Bahr, 1945).

References to cirrhosis in India, Ceylon, and China are given in Ratnoff and Patek's (1942) review. A striking feature of tropical cirrhosis is the high incidence in children and the relative frequency of recovery, even when the disease has reached the ascitic stage. The hepatic lesions have generally been attributed to the interplay of malnutrition and infection, and no clear line has been drawn between portal cirrhosis and postnecrotic fibrosis. In Jamaica, where infantile cirrhosis of the liver is common, it has been noted particularly in the children of mothers who, generally being unmarried, have to support themselves and their babies by working in the urban areas or on plantations or elsewhere. Breast-feeding, therefore, is scanty, and the infant's diet consists mostly of carbohydrate—e.g., arrowroot, cereal gruel, or even sugar and water. There is a suggestion that the disease is less frequent in fishing villages, where protein intakes may be higher (McFarlane and Branday, 1945; Platt, 1946).

Throughout Africa there occurs a condition known as infantile pellagra, or "kwashiorkor." It is found in infants, and to a less extent in adults, who are fed on bulky vegetarian low-protein diets, and it is characterized clinically by oedema, pellagrous skin lesions, steatorrhoea, and macrocytic anaemia (Trowell and Muwazi, 1945). At necropsy or biopsy an extreme degree of fatty infiltration of the liver is found (Smith, 1943), and there is no doubt that this fatty liver is eventually followed by cirrhosis. Gillman (1944) noted that cirrhosis and cancer of the liver are especially prevalent among South African negroes, and he showed that cirrhosis and necrosis of the liver occurred in rats who were fed on the South African native diet. He concluded that recurrent attacks of malnutrition resulted in progressive hepatic damage. Subsequently the Gillmans (1945) showed by serial liver punctures of patients that the fatty infiltration responded slightly to liver extract and was completely cured by desiccated stomach in a dosage of 10 g. a day. It seems unlikely that the lipotropic action of desiccated stomach is entirely due to its choline content. With the technique of liver puncture and sternal puncture, and the introduction of pure factors such as choline, methionine, and folic acid, this whole field is now wide open to research, and we shall not have long to wait for the first harvest.

Dietary Protection Against Hepatic Disease in Man

It has been believed for many years, and probably with reason, that carbon tetrachloride and arsenicals are more likely to damage the liver when the patient is undernourished, but no precise data are available. Beattie (1943–4) has claimed that during antisyphilitic treatment with arsenical drugs the incidence of liver damage can be reduced significantly and the time of greatest liver damage can be postponed by the administration of casein digests, cystine, and methionine. Experiments of this kind are complicated by the virus of homologous serum jaundice and by the reduction of the antispirochaetal activity of the arsphenamine by the sulphur compounds.

During the war the low incidence of infective hepatitis in coloured troops and native races was the subject of frequent comment, but less notice was taken of the high mortality they suffered. I have previously mentioned an outbreak in Belgian colonial troops, with a mortality of 4% (Witts, 1944). In 1943 a very high mortality was recorded in a small epidemic among some African labourers in Uganda who were in a poor state of

nutrition; of 14 cases admitted to hospital, all died.[1] Figures on the incidence and mortality of infective hepatitis in India Command during 1944 were collected by Lieut.-Col. Stuart McDonald.[1] These figures showed the usual difference between officers and other ranks. In addition they showed that the incidence of jaundice was five times as high in British troops as in Indian troops, but, on the other hand, the mortality was five times as great in the Indians as in the British. In the final issue British troops and Indian troops had an equal chance of dying of jaundice. There is some evidence that while malnutrition favours bacterial infection it antagonizes infection by viruses (Foster *et al.*, 1944). There was a good deal of anaemia and malnutrition among Indian troops.[2,3] One cannot say whether the low incidence in Indians was due to nutritional factors or to previous exposure, but there is a strong suggestion that the relatively high death rate was due to malnutrition.

Discussion

A survey of the animal experiments leaves us in little doubt as to the importance of the lipotropic factors and the thio-amino-acids to the health of the liver. An excessive intake of fat will be harmful to the liver unless it is balanced by a corresponding increase in lipotropic factors, while a high-carbohydrate regimen helps by sparing the reserve stores of protein in the liver and providing easily available energy. Proteins supply the essential methyl and sulphydryl groups, but they may also contain harmful residues which are badly tolerated in acute and chronic liver disease. Milk proteins appear to be innocuous in this regard, whereas meat and meat extracts are harmful. Choline and lecithin are present in most animal and plant tissues, and the thio-amino-acids are particularly well represented in the proteins of milk.

The most important lipotropic factors are those which provide the labile methyl groups for the manufacture of phospholipins, without which fat transport comes to a standstill. Excess of fat in the liver leads to a gradual pressure atrophy of the cells and portal fibrosis, and it also accentuates the effect of the many toxic substances which are more soluble in fat than in water. Tropical cirrhosis and alcoholic cirrhosis of the liver in man appear to be due mainly to a deficient intake of lipotropic factors, but in both disorders a toxic factor is still suspected by many people.

The effects of a deficiency of protein sulphur are more subtle and profound. The sulphydryl groups are attached to the vital enzyme systems in the liver. Protein starvation depletes the liver of these sulphur-rich components, and if the process goes far enough the cell must die. Methionine and cystine are rapidly incorporated in the depleted liver to make good the deficiency. Chloroform and arsenicals disturb the enzyme systems, presumably by combining with or neutralizing the sulphydryl groups. The disturbance is reversible within the first three or four hours of administration of the poison, but after that methionine is no longer effective, and it is clear that viable liver cells are essential for the rapid uptake of methionine. Chloroform combines with the sulphydryl groups to form the non-toxic mercapturic acids. The action of arsenicals has been reviewed by Peters, Stocken, and Thompson (1945), who showed that they have a selective action upon the pyruvate enzyme system and that an essential sulphydryl component of the protein constituent of the system is attacked. As a result of their studies they introduced the dithiol compound BAL, which prevents the toxic action of arsenic and some of the heavy metals if given before the administration of the poison and neutralizes it if the toxicity is not too long established.

Himsworth and Glynn (1944b) in their paper on toxipathic and trophopathic hepatitis have tried to integrate these data, and have suggested that in the final issue hepatic necrosis is always nutritional in origin, always due to a deficiency of essential factors. This deficiency may be primary, or it may be secondary to the increased metabolism, the swelling of the liver, and the disturbance of the circulation which result from infection or poisoning of the liver. The argument is an ingenious one, but it does not get us very far. The liver can be protected against poisons such as chloroform and arsenic by simple chemicals such as sodium thioglycollate and BAL, which act as rather specific antidotes, and it is unlikely that the results obtained with chemical poisons can be transferred without change to the action of biological toxins and viruses. In the latter conditions thio-amino-acids may act, if they act at all, by providing sulphydryl groups attached to the appropriate amino-acid residue for re-synthesis of essential sulphur proteins which have been inactivated, rather than by neutralizing the noxious agent.

[The second lecture, with a list of references, will appear in our next issue.]

[1] Unpublished reports to M.R.C. Jaundice Committee.

[2] Report on Investigations on Anaemia in the Indian Soldier from the Anaemia Investigation Team, G.H.Q., India, 1943–5; New Delhi, 1945.

[3] Proceedings of the Central Command Conference on Anaemia, held at Agra on Nov. 20 and 21, 1944; Benares, 1945.

OBSERVATIONS ON PLAGUE MENINGITIS

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Meningeal involvement in plague has occasionally been recorded, the earliest reports apparently being by the German Indian Plague Commission of 1897 and the Austrian Commission of the same year. These are cited by Meyer, Connor, Smyth, and Eddie (1937) in their review of most of the recorded cases of plague meningitis up to that year, while they discuss in detail their own case of "chronic relapsing latent meningeal plague" in California occurring in a patient whose illness began with an axillary bubo. Since then further cases have been reported, including one from Uganda by Burton and Hennessy (1940) of "subacute or chronic plague terminating in haematogenous meningeal infection," and four cases of plague meningitis complicating bubonic plague from South America by de Villafañe Lastra and Rodeiro (1942).

A particularly rare clinical form—primary plague meningitis—was reported from Dakar by Lafont, Lecomte, and Heckenroth (1915). Williams (1934) had a similar case in East Africa; and Lewillon, Devignat, and Schoetter (1940) reported still another from the Belgian Congo. These cases, like the one described in this paper (Case VIII), presented the common clinical features of meningitis with no bubo formation. In China Pollitzer (1946) has observed meningeal involvement in most recent outbreaks. In this connexion, therefore, it seems worth while to record eight cases of meningitis in a series of 203 cases of plague admitted to the General Hospital, Chuanchow, South China, during the years 1943–5.

Symptomatology

In all except one of our cases (No. VIII) meningeal involvement was a complication of pre-existing bubonic plague, symptoms appearing at the earliest on the ninth and at the latest on the seventeenth day of the disease. The clinical features closely resembled those of cerebrospinal fever or other acute meningitis. Headache, painful stiffness of the neck, and Kernig's sign appeared early and prominently. Special symptoms included convulsions (Cases III, VIII), cranial-nerve affection

(IV, V), vestibulo-cerebellar symptoms (VII), deep coma (II), and vasomotor crisis (III). Case VIII, differing from the rest, presented as a pyrexial illness with signs of meningeal irritation, no buboes or other signs being found. There was a coincidental malarial infection. The clinical picture was that of primary plague meningitis.

On lumbar puncture the pressure of the cerebrospinal fluid was as a rule raised; the fluid was cloudy, and in some cases of a canary-yellow colour. Other changes resembled those of an acute suppurative meningitis: polymorphonuclear leucocytosis, increased protein, and disappearance of sugar. *Pasteurella pestis* was found in the cerebrospinal fluid in five cases by smear and/or culture. Examination of the blood revealed a marked polymorphonuclear leucocytosis with absence of eosinophil granulocytes. All the cases were fatal, development of internal hydrocephalus being the probable cause of death. The longest period of survival was 29 days from the onset of the disease.

Pathology

Post-mortem examination in one case (No. VIII) revealed the following:

Body wasted; no petechial or skin lesions.

Brain: Marked congestion; convolutions and sulci flattened; softening of all brain tissue. Thick canary-yellow fibrino-purulent exudate covering most of the external surface, especially the parietal and frontal lobes, temporal pole, Sylvian fissure (spreading along middle meningeal artery), base of brain (especially cisterna basalis) involving all the cranial nerves, roof of fourth ventricle (cisterna magna), and the inferior, posterior, and superior surfaces of the cerebellum in the midline. Ventricles, especially the lateral ventricles, greatly dilated, with thinning of overlying brain tissue, containing a considerable quantity of yellow slightly turbid fluid—i.e., marked degree of internal hydrocephalus. Spinal Cord: Marked congestion; fibrino-purulent exudate less pronounced, but very thick in cauda equina region, matting together cord and nerve roots into a jelly-like mass (cf. "dry" lumbar puncture).

Glands: Cervical, axillary, inguinal—reddish-brown on section, congested, not enlarged. Spleen: Enlarged soft "septic" spleen; diffluent dark-red jam-like cut surface. Liver: Soft, slightly congested; noticeable cloudy swelling. Heart: Patchy congestion of epicardium; cloudy swelling of myocardium; fibrinous exudate adherent to contact margins of cusps of mitral valve (fibrinous endocarditis). Lungs: Pink, float in water; pleural surfaces smooth, shiny, patchy congestion; section revealed general congestion; no consolidation or other pneumonic signs. Kidneys: Pale; cloudy swelling of cortex; congestion of medulla. Suprarenal Glands: Pale cortex; moderately distinct pigment zone; congested medulla. Testis, Epididymis (both sides): Marked congestion; large clear hydrocele on right, small hydrocele on left. Alimentary Canal: Outwardly normal; not specifically examined. Pancreas, Thymus: Pale, apparently normal.

The presence of pericardial, pleural, and peritoneal fluids was unfortunately not looked for. In smears from the spleen numerous *Past. pestis* were found. Only a few organisms were discovered in the meningeal exudate, while smears from the liver, blood, and fibrinous exudate on the cardiac valve were negative for *Past. pestis*.

Diagnosis

The clinical diagnosis of meningitis occurring as a complication of bubonic plague ("secondary plague meningitis") presented little difficulty. Cases in which *Past. pestis* was not found in the cerebrospinal fluid (V, VI, VII) were confusing, with the possibility in our minds of the meningeal process being allergic in nature, from initial serum administration. In contrast, the other findings in the cerebrospinal fluid, especially the absence of sugar, pointed almost certainly to acute infection with pathogenic organisms, these presumably being *Past. pestis*. But the whole morbid process in these cases so closely resembled that found generally in the series that there was little reason to doubt their plague nature. Case VIII was not suspected of being plague until culture of the cerebrospinal fluid proved the presence of *Past. pestis*.

Treatment

Bubonic Plague.—The mainstay in many cases in 1944 and most cases in 1945 was oral sulphathiazole. The total amount given to each patient was usually over 50 g. Anti-plague serum was given in most cases in 1945—40 ml. intravenously on each of the first five successive days. Other treatment was mainly symptomatic.

Plague Meningitis.—With the onset of meningitis sulphathiazole was restarted if it had already been stopped. Anti-plague serum was injected intrathecally in most cases, but it was suspended or withheld in some others (III, IV, VI) where doubt existed at the time as to the nature of the morbid process. Daily lumbar puncture for drainage of the subarachnoid space was the rule, while cisternal puncture was performed in some instances if the former was unsatisfactory.

Discussion, with Special Reference to Pathogenesis

The thick fibrino-purulent exudate found over the brain and spinal cord during the necropsy on Case VIII may be presumed to be present in the other cases as well. A similar exudate and distribution were found by Meyer *et al.* (1937) in their case, but the lateral ventricles were involved while the spinal cord was free. Other similarities included the presence of internal hydrocephalus, the enlargement of the spleen, and the negative findings in the lymph nodes. It is possible that such an exudate would tend to hold back the organisms in its meshes, making difficult their recovery on examination of the cerebrospinal fluid. Negative findings in smear and culture were noted on initial lumbar puncture by Meyer *et al.*, and also in another case reported by Rivoalen and Montagne (cited by Meyer *et al.*). It is regrettable that no cultures could be made in two of our cases (V, VII) where the smear was negative or doubtful. In Case VII, while no typical plague bacilli were found in the smear, organisms having the appearance of Gram-negative diplococci were present. The possibility of mixed infection with meningococcus or of a secondary invasion of the meninges by this or other member of the *Neisseria* has to be taken into consideration, but such assumptions are not very likely. It is more probable that the organisms seen in this instance were atypical plague bacilli appearing in the "coccoid" form.

The pathogenesis of our own and other cases of primary plague meningitis is difficult to explain. That infection may be due not to invasion through the blood stream but to droplet infection as in cerebrospinal fever is altogether unlikely. Our patient had not been in contact with pneumonic plague. Conversely, supposing the disease to be a variety of primary septicaemic plague, this latter disease, in China at least, is a rapidly fatal one, so that there would be no time for localization in the meninges to take place even if that tendency were present.

Under such circumstances one is led to wonder whether these patients, supposed to be suffering from primary plague meningitis, have not in fact, at some stage of the disease, a bubo. According to Pollitzer (1945) there are really four varieties of bubonic plague: (1) pestis minor; (2) well-marked bubonic infection not leading to secondary septicaemia; (3) bubonic affection followed by secondary septicaemia; and (4) a form characterized by most serious general (septicaemia) symptoms combined with but slight affection of the lymph glands, which obviously have early failed in their attempt to hold back the invading organisms. One can conceive of the gland process being overlooked in this last variety (which incidentally represents a transition stage to primary septicaemic plague), especially if, as happened in our case, the patients are not under close observation throughout the course of the illness; in which circumstances, should meningitis develop, the clinical presentation of primary meningitis is obtained.

Factors which may have influenced the development of meningitis in our cases may thus be tabulated:

Case No.	Age (years)	Sex	Localization of Buboes	Time of Appearance of Meningeal Process	Time of Death
I	4	M	Cervical	12th day of illness	12th day of illness
II	26	M	Axillary	9th " "	22nd " "
III	40	F	"	10th " "	22nd " "
IV	37	M	"	16th " "	19th " "
V	28	M	Inguinal	12th " "	14th " "
VI	16	M	"	17th " "	29th " "
VII	39	F	Epitrochlear and axillary	15th " "	17th " "
VIII	1/12	M	—	?	17th "

So far as these figures go, males seem to be more susceptible; age appears to play no part. It should be noted in this connexion that bubonic plague in China is usually most frequent among young adults. Only two of seven patients with manifest bubonic plague had groin buboes, whereas this localization is present in at least 60% of plague sufferers in general. This is in keeping with the generally accepted view that inguinal bubonic plague is less dangerous than axillary or cervical forms.

The course of illness in all these patients was longer than is usual in plague, and symptoms of meningitis invariably appeared late in the disease. Bearing in mind that (1) the incidence of meningeal complications was much higher among our patients compared with that in other recent outbreaks in China, and (2) we were able to treat many of our patients more energetically than was possible elsewhere, we wonder whether our therapeutic measures did not facilitate meningeal involvement by prolonging the course of illness in those patients who would otherwise have died earlier. The accompanying table, showing the amount of "specific" drugs used in the treatment of plague during the years under review, supports this assumption.

Year:	1943	1944	1945
Total No. of plague cases	88	46	69
No. of cases of secondary plague meningitis:	1	2	4
Anti-plague serum used (ml.):			
Total (approx.)	920	1,530	6,330
Per patient	10	33	92
Sulphathiazole used (g.):			
Total (approx.)	—	390	2,250
Per patient	—	8	33
Sulphapyridine (I.M. suspension) used (g.):			
Total (approx.)	327	2	—
Per patient	4	—	—

NOTE.—Patients dying soon after admission received little or no specific treatment; this considerably lowers the figures for the average amount given per patient.

For the treatment of plague in general, including the prevention of meningeal complications, more effective means are called for. Wagle (1944) found sulphadiazine to be superior to sulphathiazole; our own recent experience agrees with this. Sodium sulphadiazine given parenterally should be still more effective during the initial stages of particularly severe infection. According to Pollitzer (1946), streptomycin is also a most promising new therapeutic agent. Whether and how far it will be advisable to combine these new methods of treatment with serum administration remains to be seen.

Finally, it should be stated that in Chuanchow the shortage of drugs was severe in 1943 and 1944, while the exigencies of wartime China made the clinical and pathological study of these cases obviously incomplete.

Case Reports

[The following is a key to the abbreviations used in the case notes below:—Aspn.: Aspiration of bubo, with examination of smear. C.: Culture. I.M., I.V., I.Th.: Intramuscular, intravenous, intrathecal routes. L.P.: Lumbar puncture, thecal drainage (cells: cells in C.S.F. per c.mm.; G.: globulin; S.: sugar). Serum: Anti-plague serum. Sulphath.: Sulphathiazole. Sulphap.: Sulphapyridine. Sulphanil.: Sulphanilamide. (These three drugs were given orally unless otherwise stated.) W.B.C.: White blood cells per c.mm. (N.: neutrophil granulocytes; E.: eosinophil granulocytes; B.: basophil granulocytes; L.: lymphocytes; M.: monocytes).]

Case I: Primary Skin Plague; Cervical Bubonic Plague; Secondary Plague Meningitis

Male aged 4; seen 3/7/43, giving a history of one day's high fever, diarrhoea, tender swelling rt. side of neck. T. 103° F. (39.4° C.); vesicle with raised dusky areola in rt. parietal region; tender enlarged gland in rt. posterior triangle. Aspn., *Past. pestis* found ++. Parents refused treatment.

Patient admitted 13/7/43. T. 105.2° F. (40.7° C.), P. 140, R. 40. Toxic, restless; large fluctuant swelling with surrounding brawny oedema whole rt. side of neck. Blood: W.B.C. 25,500 (N. 83%, L. 14%, M. 1%). The bubo was incised and drained.

Course.—14/7/43: T. 105-106° F. (40.6-41.1° C.); neck rigidity +; Kernig's sign +; L.P. Smear of C.S.F.: *Past. pestis* found. Patient died shortly after.

Treatment.—150 ml. serum (? route), 4 g. sulphanil., 5-6 g. sulphap., all before admission. After admission 30 ml. serum I.M., 10 ml. I.Th.; sulphap., 0.5 g. I.M.

Case II: Axillary Bubonic Plague; Secondary Plague Meningitis

Male aged 26; admitted 12/6/45, with history of one day's high fever, delirium, painful swelling rt. axilla. T. 104.2° F. (40.1° C.), P. 118, R. 24; tender swollen gland rt. axilla. Aspn.: *Past. pestis* not found. Clinically, typical bubonic plague.

Course.—Bubo steadily enlarged, while general symptoms improved. 20/6/45: T. 104° F. (40° C.), P. 90, R. 24; severe headache; neck rigidity +; Kernig's sign +. L.P.: turbid yellow fluid; cells 530, G. +, S. −. Smear: Gram-negative bacillus (? *Past. pestis*) found (few). C. of C.S.F.: *Past. pestis* isolated. 21/6/45: W.B.C. 11,000 (N. 83%, L. 16%, M. 1%). 22/6/45: T. 100° F. (37.8° C.), P. 80; patient much improved; bubo subsided.

25/6/45: T. 103° F. (39.4° C.), P. 90; return of pyrexia. 27/6/45: T. 102.6° F. (39.2° C.), P. 90; severe headache; neck rigidity +; Kernig's sign +. 29/6/45: L.P. C.S.F.: G. +, S. −. Smear: organisms not found. Patient becoming comatose. 1/7/45: T. 97° F. (36.1° C.), P. 70, R. 20; deep coma; pupils dilated; corneal reflexes absent; pulse, good volume. Cisternal puncture: 50 ml. cloudy yellowish fluid; cells 280, G. +, S. −. Smear: N. predominate; organisms not found. Cisternal drainage repeated same day. 3/7/45: T. 99.8° F. (37.7° C.), P. 130, R. 30; patient died (pre-mortal T. 102° F.—38.9° C.).

Treatment.—Serum 200 ml. (180 ml. I.V., 20 ml. I.M.) first 5 days; onset of meningitis to death, 220 ml. (180 ml. I.Th., 40 ml. I.V.) Sulphath. 141 g.; sodium sulphath. I.M. 2 g.

Case III: Axillary Bubonic Plague; Secondary Plague Meningitis

Female aged 40; admitted 23/6/45, with history of 3 days' fever, pain in lt. axilla. T. 102° F. (38.9° C.), P. 108, R. 24; tender swollen gland lt. axilla. Aspn. not performed. Clinically, typical bubonic plague.

Course.—24/6/45: Another bubo rt. groin. 27/6/45: T. 100° F. (37.8° C.), P. 84, R. 20; general condition improved; buboes larger. 30/6/45: T. 104° F. (40° C.), P. 100, R. 24; headache, clouded mentality; neck rigidity +; Kernig's sign +; buboes much regressed, non-tender. L.P.: cloudy fluid; cells 800, G +, S. −. Smear: N. predominate, organisms not found. 2/7/45: T. 102° F. (38.9° C.), P. 96, R. 24. L.P. C.S.F.: S. −; C., no growth. Blood: W.B.C. 16,300 (N. 91%, B. 1%, L. 8%).

10/7/45: Sudden attack of profuse sweating, flushing of face (T. 95° F. (35° C.), P. 80, R. 24). Blood: W.B.C. 6,000 (N. 80%, L. 20%). 11/7/45: Sudden onset of coma; epileptiform convulsions, prolonged and generalized, controlled with general anaesthetic, morphine, hyoscine. L.P.: canary-yellow fluid under pressure. 12/7/45: T. 100° F. (37.8° C.), P. 124, R. 30; pulse weakening, marked conjunctival congestion. Patient died. Post-mortem cisternal puncture: C. of C.S.F., *Past. pestis* isolated.

Treatment.—Serum 320 ml. (40 ml. I.Th., 280 ml. I.V.) in first 10 days. Sulphath. 35 g. in first 5 days; 54 g. from 9th to 17th day. Sulphath. suspension 8 g. I.M. between 6th and 7th days.

Case IV: Malaria; Axillary Bubonic Plague; Secondary Plague Meningitis

Male aged 37; admitted 25/6/45, with history of 3 days' chill, high fever; one day painful swelling lt. axilla. T. 104.2° F. (40.1° C.), P. 140; acute lt. axillary adenitis. Aspn.: *Past. pestis* found +++. Blood film: *Plasmodium vivax* found (few). Spleen enlarged.

Course.—2/7/45: T. 100° F. (37.8° C.), P. 84; general condition much improved; bubo very large; marked periadenitis. 5/7/45: Bubo softening. 8/7/45: T. 103° F. (39.4° C.), P. 96; bubo incised, drained. Blood: W.B.C. 26,400 (N. 93%, L. 7%). 10/7/45: T. 103° F., P. 100; patient wasted, drowsy, vomiting; facial palsy (no record which side). L.P.: opalescent fluid; cells 350, G. trace, S. −. Smear: N. predominate, organisms not found. C., *Past. pestis* isolated. 12/7/45: T. 103° F., P. 100; facial palsy disappeared, neck rigidity +. 13/7/45: T. 100° F. (37.8° C.), P. 100; comatose, subsultus tendinum; incontinence of urine; neck rigidity ++; Kernig's sign +. L.P.: cloudy yellow fluid. Smear: *Past. pestis* found ++. C., *Past. pestis* isolated. Blood: W.B.C. 17,000 (N. 91%, L. 9%). Patient died, with pre-mortal rise in T. and P.

Treatment.—Serum 200 ml.; sulphath. 127 g.; quinine bisulphate 153 gr. (10 g.).

Case V: Inguinal Bubonic Plague; Secondary Plague Meningitis

Male aged 28; admitted 10/7/44, with history of 4 days' high fever, painful swelling lt. groin. T. 105° F. (40.6° C.), P. 110, R. 40; small atypical vesicle lt. ankle; tender swollen gland in lt. groin. Aspn.: *Past. pestis* found (few).

Course.—16/7/44: T. 100° F. (37.8° C.), P. 80, R. 25; generally much improved; bubo dull red, indurated, non-tender. 20/7/44: T. 104° F. (40° C.), P. 100, R. 28; severe headache for 2 days;

frequent vomiting; sleepiness, dull mentality; neck rigidity +; Kernig's sign +; lt. external rectus palsy. Blood: W.B.C. 18,400 (N. 97%, L. 3%). L.P.: canary-yellow cloudy fluid released under high pressure; cells 5,060, G. +, S. —. Smear: N. predominate, no organisms found. Patient passed into coma, with weakening pulse, sluggish pupils, general flaccidity, and died.

Treatment.—Serum 200 ml. (195 ml. I.V., 5 ml. I.M.) first 6 days; after onset of meningitis, 10 ml. I.Th., 20 ml. I.V. Sulphath. 29 g. first 4 days; later 5 g.

Case VI: Inguinal Bubonic Plague; Secondary Plague Meningitis

Male aged 16; admitted 15/6/45, with history of 2 days' chill, fever, painful swelling rt. groin. T. 103° F. (39.4° C.), P. 120, R. 25; tender swollen rt. inguinal gland. Aspn.: *Past. pestis* found (few).

Course.—General condition gradually improved; bubo steadily enlarged. 24/6/45: T. 103° F., P. 90, R. 24; commencing suppuration in bubo. 27/6/45: T. 103° F., P. 90, R. 24; bubo incised, drained. 30/6/45: T. 102° F. (38.9° C.), P. 90, R. 24; headache, clouded mentality; neck rigidity +; Kernig's sign +. L.P.: cloudy fluid; cells 1,000, G. +, S. —. Smear: N. predominate, organisms not found. 1/7/45: Neck more rigid, with head retraction, opisthotonos; deafness.

2/7/45: Symptoms improved. L.P.: C.S.F. cloudy, yellow; S. —; C., no growth. Blood: W.B.C. 9,000 (N. 88%, L. 12%). 3/7/45: T. 98° F. (36.7° C.), P. 90, R. 24; further improvement. 5/7/45: T. 100° F. (37.8° C.), P. 100, R. 24. Patient insisted on leaving hospital, and died about a week later.

Treatment.—Serum 200 ml. I.V. in first 5 days; onset of meningitis onwards, 60 ml. I.Th., 20 ml. I.V. Sulphath. 52 g. in first 8 days; onset of meningitis onwards, 20 g.

Case VII: Epitrochlear and Axillary Bubonic Plague; Secondary Plague Meningitis

Female aged 39; admitted 28/7/44, with history of 2 days' high fever, painful swelling at lt. elbow and lt. axilla. T. 102.4° F. (39.1° C.), P. 104, R. 26; acute lt. epitrochlear and axillary adenitis with periadenitis. Epitrochlear gland aspn.: *Past. pestis* found +. Blood: W.B.C. 10,400 (N. 84%, L. 15%, M. 1%). Urine: moderate albuminuria, few pus cells.

Course.—Pyrexia maintained; buboes increased in size; oedema of whole limb down to fingers. 9/8/44: W.B.C. 16,900. 10/8/44: T. 103° F. (39.4° C.), P. 100, R. 30; buboes and oedema subsiding. Onset of painful stiff neck, headache, marked vertigo, relieved by keeping eyes shut, vomiting. Neck rigidity +; Kernig's sign +. Eyes: fine rotatory nystagmus on looking to lt., coarse jerking nystagmus on looking to rt. L.P.: clear fluid; cells 210, G. +, S. —. Smear: N. predominate; "Gram-negative diplococcus" (?) found. Urine: slight albuminuria. 12/8/44: Clouded mentality; irritability, nausea, severe vertigo, tinnitus; nystagmus pronounced, jerking, especially on lateral deviation; limbs flaccid; incoordination in finger-nose test on lt. L.P.: clear fluid; cells 500, G. +, S. —. Smear: N. predominate, no organisms found. Patient passed into coma and died.

Treatment.—Serum 200 ml. I.V. first 4 days. Sulphath. 37 g. 7 days beginning 31/7/44. Onset of meningitis: sulphath. 4 g., sulphap. 9 g., anti-meningococcal serum 20 ml. I.M.

Case VIII: Malaria; Primary Plague Meningitis

Male one month old; admitted 9/7/45, with history of 4 days' fever and slight convulsive movements. T. 104.4° F. (40.2° C.); irritable; fontanelle tense; slight neck rigidity; Kernig's sign equivocal. Blood: W.B.C. 17,000; film: *Plasmodium vivax* gametocytes found (few).

Course.—L.P. attempted many times without success. 12/7/45: T. 103° F. (39.4° C.); slight jaundice; neck rigidity +; Kernig's sign —. L.P.: few ml. turbid yellow fluid; cells 400, G. +, S. —. Smear: Gram-negative bacillus found (? *Past. pestis*). C.: *Past. pestis* isolated. 15/7/45: T. 99° F. (37.2° C.); head retraction; Kernig's sign +. 19/7/45: T. 100° F. (37.8° C.); pale, wasted; epileptiform convulsions, especially rt. face. 21/7/45: T. 101° F. (38.3° C.). L.P.: bead of pus at end of needle. Smear: Gram-negative bacillus found (? *Past. pestis*). (L.P. performed repeatedly from 12/7/45 onwards had only "dry" result.) Convulsions generalized, frequent; patient died 22/7/45.

Treatment.—Sulphap. 1.5 g. first 3 days, repeated last 2 days. Sulphath. 8.125 g., commencing 4th day, for 7 days. Serum 50 ml.

Summary

Eight cases of plague meningitis are described, occurring in a series of 203 cases of plague treated in South China during the years 1943–5.

The occurrence of a rare clinical form—primary plague meningitis—is recognized; one case is described and its pathogenesis discussed.

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"SULPHA-COMBINATION"—A NEW CHEMOTHERAPEUTIC PRINCIPLE

BY

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The commonly used sulphonamides—sulphathiazole, sulphadiazine, and sulphamerazine—have on the whole the same effect when employed clinically. The two pyrimidine compounds, however, are less toxic than sulphathiazole, and are therefore better tolerated. From the therapeutic point of view sulphonamide treatment might be regarded as more or less perfect if it were not attended by the risk of damage to the blood and kidneys. Toxic effects on the blood are, however, extremely rare with the above-mentioned drugs. Renal complications are more common: they may have a toxic or allergic origin, but in most cases are due to a deposition of the sulphonamide compounds, or their acetyl derivatives, in the tubules from supersaturated solutions. This risk can be reduced by the introduction of acid-binding media and the maintenance of a high diuresis. With these precautions renal complications are rare, but the risk remains, and for this reason inadequate and ineffective doses are often given. Thus the importance of reducing concrement formation is evident.

Provided that the sulphonamides do not affect each other's solubility but dissolve independently, which is to be expected from the chemical point of view, the risk of concrement formation might be reduced if, for the attainment of a certain blood concentration or effect, not merely one compound but a mixture of several equivalent sulphonamides was employed. From the clinical standpoint it cannot make any difference if several compounds are used instead of one when all the drugs are equally effective. The risk of concrement formation will, however, be reduced in this case, since each drug in the mixture is present in a considerably lower degree of saturation than when a single compound is employed. This new therapeutic principle we have named the "sulpha-combination principle."

In cases where it is desired to increase the dose beyond the normal limits, resulting in higher blood concentration and better therapeutic outcome, the same principle can be applied. If in such cases a single compound is used the risk will be increased. On the other hand, when a mixture of several drugs is employed the risk will be reduced. The method has been used in a preliminary form (a mixture of equal parts of sulphathiazole and sulphadiazine) in Sweden for more than three years in the treatment of gonorrhoea (Hagerman, 1944; Herlitz, 1944; Werkö, 1945). In spite of the very high dosage (12 g. a day for four days) remarkably few renal complications occurred (Nilzén, 1946a).

The most important problem is how to avoid formation of renal obstruction with a normal dosage. A mixture of sulphathiazole and sulphadiazine, also suggested by Lehr (1945), is not, however, ideal. The chances of renal complications are admittedly reduced, but they are not eliminated, since some of the excretion products are still supersaturated. If this is to be avoided the two above-mentioned compounds must be complemented with a third—for example, sulphamerazine.

In the following account we discuss all the questions connected with "sulpha-combination" and describe experiments showing the practicability of the method. We also give an account of our final mixture, prepared according to this principle—"sulphadital"—which contains the three compounds sulphathiazole, sulphadiazine, and sulphamerazine, equally active in clinical practice. The present article is a condensation of a larger work which has already been published in Swedish (Frisk *et al.*, 1946).

Solubility

The solubility of sulphathiazole, sulphadiazine, sulphamerazine, and the corresponding acetyl derivatives was determined in solvents saturated with the substances separately and with mixtures of from two up to all six compounds. The solvents used were 1/30 molar potassium sodium phosphate buffer and urine varying in *p*H. The substances were brought into solution by even mechanical shaking for twenty-four hours at constant temperature—37° C.—and with the solutes present in excess. The concentrations were then determined in a photo-

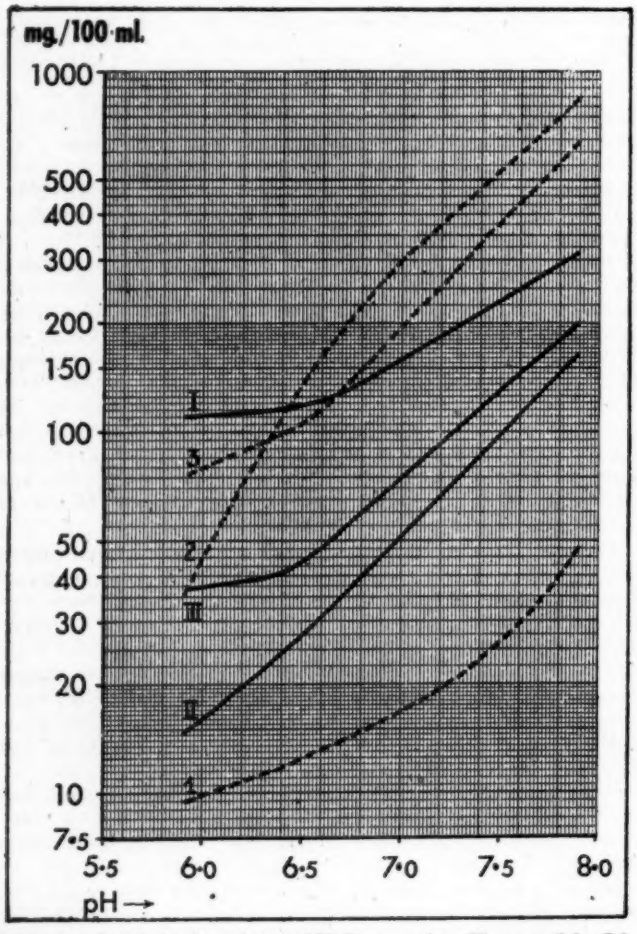

FIG. 1.—Solubility in urine at 37° C. over the *p*H range 5.9–7.9. I = sulphathiazole. II = sulphadiazine. III = sulphamerazine. 1 = acetylsulphathiazole. 2 = acetylsulphadiazine. 3 = acetylsulphamerazine.

electric colorimeter according to Bratton and Marshall (1939). The solubility is given in mg. of dissolved substance per 100 ml. of solvent. The solubility curves are drawn to a logarithmic scale.

For reasons of space we give here only the solubility in urine. Figs. 1 and 2 show the solubility at *p*H 5.9–7.9. From these it appears that the three sulphonamides, their acetyl derivatives, and all six compounds are, as expected, dissolving independently of one another.*

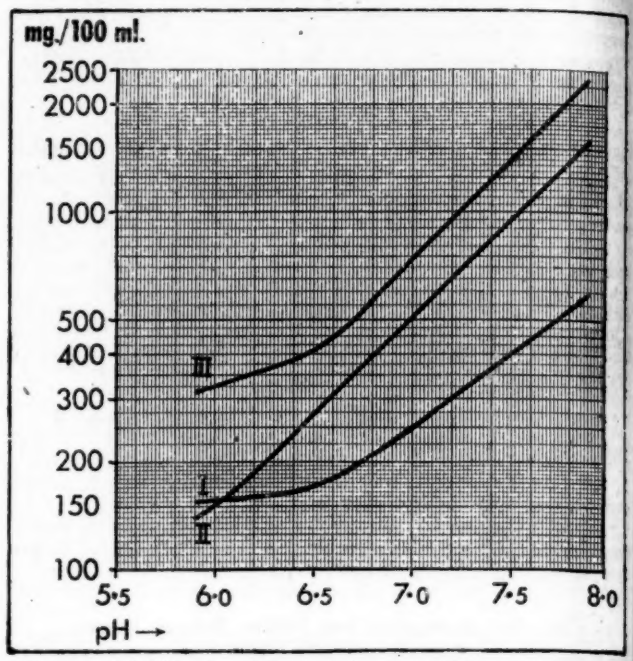

FIG. 2.—Solubility in urine at 37° C. of different mixtures over the *p*H range 5.9–7.9. I = sulphathiazole + sulphadiazine + sulphamerazine. II = acetylsulphathiazole + acetylsulphadiazine + acetylsulphamerazine. III = Σ sulphonamides + Σ acetyl derivatives.

Concrement Formation

We do not propose to review here the comprehensive literature on renal complications during sulphonamide treatment clinically observed or studied in animal experiments. Two main types of injury to the kidney can be distinguished—namely, those of toxic or allergic origin, and those due to the formation of calculi. In the first-mentioned type, which is more uncommon, small areas of focal necrosis are found not only in the tubular cells of the kidneys but also in other organs, as well as vascular changes, with fibrinoid degeneration of the media and voluminous intima proliferations.

The changes occurring after calculus formation are localized to the distal part of the kidney, and are characterized by distended tubules filled with masses consisting of protein precipitate, desquamated cells, and crystals of the sulphonamides or their acetyl derivatives. More detailed descriptions of the various anatomical changes have been given by Murphy *et al.* (1944), Bergstrand (1946), and others.

In the present investigation the formation of renal calculi has been studied after the administration of sulphathiazole, sulphadiazine, and sulphamerazine. The dose and the blood concentration, as well as the time required to produce obstruction, have been determined for each compound. The composition of our mixture—"sulphadital"—was decided on the basis of these results, and with due respect to the solubility and pharmacological properties of the constituent compounds. This preparation was then subjected to the same investigation in order to ascertain whether the risk of concrement formation had been diminished by the combination.

Rabbits were used for the experiments. They were given a vegetable diet but no water. The urine was acid (*p*H 4–6). The compounds were administered intraperitoneally morning and evening (eight hours between the doses) every day except Sundays. The animals that did not die spontaneously were killed after about three weeks. Those dying spontaneously usually had concrements, which were the cause of death, but in some cases they died of injuries due to the injections. Twice a week free and total sulphonamide concentrations as well as non-protein nitrogen were determined.

* Further details to be published elsewhere; see also *Nord. Med.* 1946, **29**, 639.

As soon as possible after death the kidneys were removed, fixed by freezing-drying according to Altmann, and then examined under a fluorescent microscope with the histological technique described by Sjöstrand (1944) and Helander (1945). With this procedure it is possible to make detailed studies of the preparations without staining. The crystals thus remain *in situ* in the preparations. It is also easy to detect the calculi, as they fluoresce in a characteristic manner (blue fluorescence).

With the method employed it was easy to produce renal obstructions. Their localization and the anatomical picture fully corresponded with previous descriptions. By the polarizing microscope it was also possible to verify the crystalline nature of the concrements. Melting-point determinations in polarized light showed that the sulphathiazole concrements consisted mainly of acetylsulphathiazole, and those of sulphamerazine of the unacetylated compound. As regards sulphadiazine, it was not possible to decide whether the crystals consisted of free or acetylated compound, the melting-points being too close together.

The results have been summarized in Table I. A daily dose of 0.8 g. of *sulphadiazine* per kg. body weight during a period

TABLE I.—*Summary of Results of Experiments on Concrement Formation*

Preparation	Daily Dose in g./kg.	No. of Experiments	Experimental Period in Days (mean)	Percentage Probability of Concrement	Blood Concentration during Experimental Period in mg./100 ml. (mean)	
					Free	Total
Sulphadiazine	0·8	5	9	100	18	38
	0·6	5	22	20	7	17
Sulphamerazine	0·6	5	10	100	6	28
	0·4	5	15	0	3	10
Sulphathiazole	0·8	6	16	67	6	11
	0·6	5	18	20	3	8
Sulphadital	2·0	10	12	40	41	63
	1·0	10	18	0	20	30

of nine days was necessary for provoking renal calculi in all the animals. A dose of 0.6 g./kg. seldom gave rise to concrements. In the case of *sulphamerazine* concrements were obtained in all the animals with a dose of 0.6 g./kg. in the course of only ten days, whereas a dose of 0.4 g./kg. was tolerated without any renal injuries. *Sulphathiazole* required a daily dose of 0.8 g./kg. for sixteen days (the blood concentration was remarkably low, presumably on account of the rapid excretion). In this series, however, only two-thirds of the animals died, even though a certain risk attended a dose of 0.6 g./kg. We have therefore considered this dose to be on the whole comparable to the dose of 0.6 g./kg. for sulphadiazine and 0.4 g./kg. for sulphamerazine. From this it follows that the last-mentioned compound should be present in the mixture in a smaller proportion than the two others.

Finally, it was possible with *sulphadital* to administer considerably higher doses without giving rise to concrements. With a daily dose of 2 g./kg. 60% of the animals escaped concrement formation during an experimental period of twelve days, despite the very high blood concentration. If the dose was reduced to 1 g./kg. no concrements appeared in any of the animals during an experimental period of eighteen days. The individual components of the mixture with this dosage gave rise to renal calculi in 100% of the cases.

Absorption and Excretion

With the dosage generally employed therapeutically the sulphonamides investigated here are absorbed almost completely; but with increasing oral doses the percentage absorbed becomes progressively less, as with other sulphonamides. The effect of the simultaneous administration of different sulphonamides on the absorption, excretion, and acetylation of the individual compounds was determined in the following way. Various single oral doses of sulphathiazole and sulphamerazine, separately and in a mixture, were administered to each of three healthy persons. The experimental procedure and method of determination earlier employed by Frisk (1943, 1945) were used.

Table II shows the mean blood concentrations in a typical experiment. A simultaneous administration of 2 g. of sulphathiazole and 2 g. of sulphamerazine gives a concentration that practically equals the sum of the separate values for the two compounds after a dose of 2 g.

TABLE II.—*Comparison between the Blood Concentrations after Single Oral Doses of Sulphathiazole and Sulphamerazine Separately and in Mixture*

Time in Hours	Blood Concentration in mg. per 100 ml.							
	Found						Calculated	
	After 2 g. Sulphathiazole		After 2 g. Sulphamerazine		After 2 g. Sulphathiazole + 2 g. Sulphamerazine		After 2 g. Sulphathiazole + 2 g. Sulphamerazine	
	Free	Total	Free	Total	Free	Total	Free	Total
1	2·4	2·7	2·0	2·1	5·6	5·9	4·4	4·8
2	2·8	3·2	3·0	3·0	6·3	7·0	5·8	6·2
4	2·4	3·2	3·8	4·0	7·2	8·2	6·2	7·2
6	2·1	2·7	4·1	4·7	6·6	7·6	6·2	7·4
10	1·0	1·4	3·4	3·9	4·1	5·6	4·4	5·3
24	—	—	1·8	2·4	2·0	2·7	1·8	2·4

TABLE III.—*Comparison between the Excretions through the Kidneys after Single Oral Doses of Sulphathiazole and Sulphamerazine Separately and in Mixture*

Time in Hours	Excreted Amount in Grammes (cumulative)							
	Found						Calculated	
	After 2 g. Sulphathiazole		After 2 g. Sulphamerazine		After 2 g. Sulphathiazole + 2 g. Sulphamerazine		After 2 g. Sulphathiazole + 2 g. Sulphamerazine	
	Free	Total	Free	Total	Free	Total	Free	Total
2	0·132	0·166	0·011	0·023	0·148	0·183	0·143	0·189
4	0·358	0·479	0·045	0·082	0·442	0·615	0·403	0·561
6	0·592	0·796	0·088	0·207	0·659	0·929	0·680	1·003
10	0·833	1·160	0·182	0·446	0·793	1·652	1·015	1·606
24	1·047	1·596	0·376	0·918	1·476	2·463	1·423	2·514
48	1·100	1·694	0·487	1·265	1·697	3 057	1·587	2·959
72	1·100	1·694	0·547	1·405	1·743	3·162	1·647	3·099

Table III shows the excretion of the drugs in the urine in one of these experiments. The excretion also takes place without the compounds influencing each other. Moreover, the acetylation is unaffected. For technical reasons these experiments were performed with only two drugs.

Composition of the Mixture, its Actions and Uses

Our results thus show that the sulphonamides examined, and their acetyl derivatives, do not affect each other's solubility, that a mixture of several compounds causes concrements to a considerably smaller degree than do the individual drugs at the same blood concentration, and that the compounds in a mixture are absorbed and excreted in the urine independently of each other. Since, as we have also been able to establish, the antibacterial effect of a mixture of several different sulphonamides is not affected but is the sum of the effects of the various compounds, the basis has been laid for the clinical use of the sulpha-combination principle.

A good mixture should contain a number of sulphonamides sufficient to maintain an adequate therapeutic concentration in the blood without risk of concrement formation. The compounds included in it must produce about the same antibacterial effect, be of low toxicity, and possess otherwise favourable pharmacological properties. In consideration of these factors, a mixture of sulphathiazole, sulphadiazine, and sulphamerazine is most suitable. The proportion of the different constituents depends upon their mode of absorption and excretion, their tendency to cause renal injuries, and the solubility of the compounds or their conversion products.

Sulphathiazole should not predominate in the mixture, as it is rapidly excreted and its acetyl derivative is not easily soluble. Sulphamerazine, owing to its slow excretion, gives rise to concrements in a somewhat lower dose than do sulphathiazole and sulphadiazine. The amount of sulphamerazine should therefore be less than that of the two others. The rapid excretion of sulphathiazole and the slow excretion of sulphamerazine can be compensated, however, if the drugs are present

in a certain proportion. We have sought for a mixture that has on the whole the same pharmacological properties as sulphadiazine, which involves no risk of accumulation, and which it should be possible to administer at intervals of four hours.

The final mixture (sulphadital) was given the following composition: sulphathiazole 37%, sulphadiazine 37%, and sulphamerazine 26%. The normal daily dose in the treatment of pneumonia, for example, is for sulphathiazole 6 g., for sulphadiazine 5–6 g., and for sulphamerazine 4–5 g. A daily dose of 6 g. of the above-mentioned mixture thus provides about one-third of the otherwise normal daily dose of each constituent.

Figs. 3 and 4 show the absorption, excretion, and acetylation of sulphadital after single oral doses of 2 and 4 g. (average

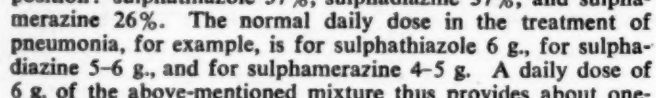

FIG. 3.—Blood concentration after single oral doses of sulphadital: the lower curves after 2 g., the upper curves after 4 g. The upper curve in each group shows the total amount of sulphadital, the lower curve the free sulphadital; the hatched area indicates the amount acetylated.

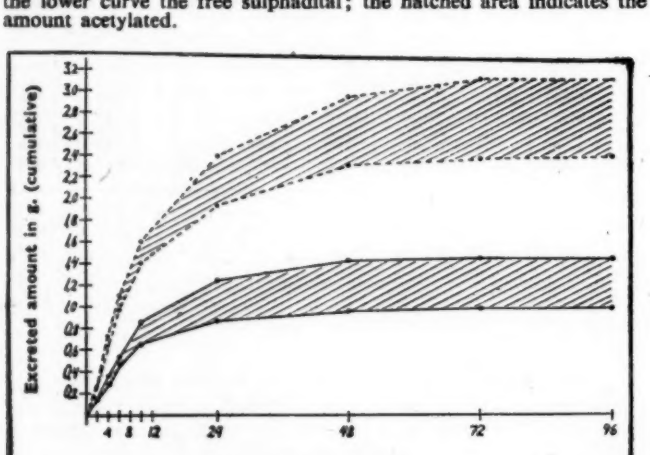

FIG. 4.—Excretion through the kidneys after single oral doses of sulphadital: the lower curves after 2 g., the upper curves after 4 g. In each group the upper curve shows the total amount of sulphadital, the lower curve that of free sulphadital; the hatched area indicates the amount acetylated.

of three experiments on the same persons). The blood concentration rises rapidly, reaching a maximum after 2–4 hours, whereafter it sinks slowly (Fig. 3). The excretion in the urine takes place relatively slowly, and after 48–72 hours is practically concluded (Fig. 4). Of the total dose administered 75–80% has then been recovered, 50–60% in an unaltered form. Thus in the urine about one-third of the amount excreted is present as acetyl derivatives.

With the following dosage—2 g. at 6 p.m., 2 g. at 10 p.m., and thereafter 1 g. four-hourly, the first dose being given at 6 a.m. and the last at 10 p.m.—the mean blood concentration (15 cases) of free sulphonamides after 15 hours was 7.8 ± 0.5 mg. per 100 ml. and that of total sulphonamides 8.5 ± 0.4 mg., the values after 39 hours being 8.0 ± 0.6 and 9.3 ± 0.7 mg., and after 63 hours 8.4 ± 0.8 and 9.1 ± 0.8 mg., respectively. These values agree well with the blood concentrations obtained when the same amounts of sulphadiazine are administered at the same times.

If the dose of sulphadital is increased to almost twice the amount—i.e., 4 g., 4 g., and thereafter 1.5 g. four-hourly—the means of the corresponding values (10 cases) are: after 15 hours 11.5 and 12.7 mg., after 39 hours 10.8 and 12.0 mg. per 100 ml., respectively. There is thus no risk of accumulation even with these high doses. Although the dose has been almost doubled the blood concentration does not increase by more than about 40%, owing to the fact that absorption is less complete when higher doses are given.

Calculation shows that the single sulphonamides at the usual pneumonia doses give such high concentrations of the free compounds and their acetyl derivatives in an acid urine that the compounds are always present in more or less supersaturated solutions. In a neutral urine this also holds for sulphathiazole, its acetyl derivative, and the free pyrimidine compounds, which may be present in concentrations two to three times greater than their solubility. At yet higher *p*H—e.g., 7.5—the risk is still less, but acetylsulphathiazole and free sulphadiazine may still be supersaturated. Considering these facts, it is surprising that renal complications appear in only a small percentage of the cases.

With the sulpha-combination drugs in the proposed normal dosage the risk of concrement formation is greatly reduced, as the components of the mixture are no longer excreted in the form of supersaturated solutions. This holds good if the reaction of the urine is neutral or approximately so. If, on the other hand, it is more acid, the concentrations of two of the excretion products—acetylsulphathiazole and sulphadiazine—may exceed their solubility. For safety's sake a high diuresis should therefore be maintained and the patient should be given acid-binding substances. We believe that if these precautionary measures are observed the risk of concrement formation in a normal kidney will be almost eliminated.

Hitherto the sulpha-combination in the form of sulphadital has been used in many hundreds of cases of acute pneumonia with good results and tolerance and without any known case of renal calculi, also with increased doses in many cases of gonorrhoea. Nilzén (1946b) has treated 105 cases of gonorrhoea with increased doses of sulphadital (9 g. daily for three days). Although he did not use any acid-binding substances no concrements were observed in any of the cases.

Summary

"Sulpha-combination," a new principle for treatment with sulphonamide drugs, is discussed, and an account is given of sulphadital, a preparation made according to this principle and composed of sulphathiazole, sulphadiazine, and sulphamerazine.

The results are given of a number of experiments illustrating the practicability of the method.

The importance of "sulpha-combination" is twofold. First and foremost, it appears to eliminate the risk of concrement formation at a normal dosage. Secondly, in cases with more resistant bacteria the doses may be considerably increased without greater risk of calculus formation than is possible with a single compound.

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Medical practitioners who are asked to give vaccinations and inoculations to intending air passengers are particularly requested to use the "International Certificate of Inoculation and Vaccination" (Form 3150) when recording them. These forms can be obtained by the passenger from the agency from which he receives his ticket and flight information. The use of any other form of certificate is liable to lead to delays and possibly to quarantine in foreign countries where the international certificate is the only certificate officially recognized.

ENDOGENOUS DEPRESSION IN GENERAL PRACTICE

BY

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In six years of practice before the war I diagnosed only one case of endogenous depression, and that after the patient had committed suicide. After psychiatric experience in the Army I have found the condition comparatively common in general practice. In six months no fewer than 20 cases have come under my care, pointing to the prevalence of the complaint. Not many family doctors have the opportunity for postgraduate study of psychiatry, and the result must be that a great many cases go undiagnosed. Only a small proportion of the cases, usually the most serious, come before a psychiatrist, as the fear of mental-hospital stigma keeps the patient away from specialist help until either the case is certifiable or time itself has effected a cure.

This paper is a preliminary report to draw attention to the endogenous depression which is far more common than is generally realized. The term "endogenous" is used in preference to the term "psychotic" as the latter implies insanity, and few of the patients found in general practice could be certified as insane. Of the 20 cases in this paper only three were considered bad enough for electro-convulsive therapy (E.C.T.). All three stubbornly refused to go to a mental hospital for treatment. Two have recovered without it, but the third is showing no signs of improvement.

One seldom hears of a patient with cancer committing suicide. On the other hand, suicidal ideas are common among the depressives. The desire to end things is some measure of the patient's suffering. Depression is probably the most unpleasant illness anyone can contract. With such deadly diseases as cancer or tuberculosis there is always some hope, real or built on euphoria; but to the depressed patient, whose condition is far from hopeless, there is no hope and no future.

The mental hospital cases with a general retardation of the psychological and motor systems are fairly easy to diagnose; but for each classical case there are a score of mild depressives who eke out a miserable existence in their homes, keeping their troubles to themselves or receiving the only treatment a family doctor can offer, which is often inadequate. Others are wrongly diagnosed as neurotics, hypochondriacs, and other chronic forms of invalidism. An accurate diagnosis is important, as there is always the danger of suicide. The patient is often reluctant to talk about his feelings and is easily put off by unsympathetic handling. He is only too ready to attribute blame to himself. Thus to be scorned as a neurotic or simply told to "pull himself together" is both cruel and unfair. Frequently his relations have tried these "back-slapping" methods, implying that he is either soft or weak-willed. No patient in practice deserves more sympathy. Good rapport, if it can be established between the patient and his doctor, is one of the most valuable weapons with which to treat the disease. Once adequate rapport has been created, such difficult subjects as suicide, the nature of the illness, and the possibility of mental hospital treatment can all be discussed with pleasing candour. The patient may show surprise when such subjects are broached, but he is rarely upset by them, because in his heart he has already weighed up such possibilities. "I have thought of suicide, but I should never have admitted it if you had not asked me," is the typical reply to such a question.

Symptoms

The disease is largely symptomatic and it can simulate almost any functional or organic illness. There is an almost infinite variety of types. The following symptoms are the most important, and each will be considered in detail. (*a*) depression; (*b*) suicidal ideas; (*c*) changes in the sleep rhythm; (*d*) changes in habit and outlook; (*e*) obsessions and phobias.

Depression

In the type of case one deals with in general practice this is rarely profound, and one cannot always see it written on the patient's face. Close relations usually notice some difference. The patient as a rule complains of one or more somatic symptoms and admits of depression only when questioned directly. The varieties of early symptoms are shown in the accompanying Table.

The patient will usually admit that he is depressed and that his outlook on life has changed. His sense of humour is different from what it was and he rarely laughs. Life has become a burden and every molehill looks like a mountain. Problems and responsibilities he would once have taken in his stride now make him hesitate and hold back. He has lost confidence in himself and his ability. When asked if he or his

Table Showing Varieties of Early Symptoms

Case No.	Sex	Age	Previous Attacks	First Symptom	Sleep	Suicidal Urge	Habit Changes	Work	Length of Illness	Result
142	M	25	None	Patient had malaria	Normal	Present	Asocial	Put off work	3½ months	Recovered
143	F	47	"	Insomnia	Early waking and bad dreams	None	"	Carried on in a fish-shop	5 "	"
144*	M	60	Recurs each spring	Depression	Early waking	"	"	A chronic invalid	2 "	"
145	F	27	None	"	General insomnia	"	None of note	Kept at work	5 weeks	"
146	F	46	One previous attack	Patient had cut flexor tendon	Difficulty in falling asleep; sleep broken	"	Seeks company; fears to be alone	Off work	10 months	I.S.Q.
147	F	43	None	Fainting	General insomnia	"	Has stopped playing piano	Kept on at housework	8 "	Improving
148	F	60	"	Pain in chest	"	Present	Weeping bouts	"	3 years	Recovered
149*	M	38	"	Indigestion	Difficulty in dropping off	Marked at times	Asocial	Off work	8 months	"
151	F	51	"	Wind in stomach	Broken sleep and dreams	Present	Weeping bouts	Kept on at housework	2 years	I.S.Q.
152	M	45	"	"	Early waking	None	Asocial	Work modified	3 months	Recovered
157	F	53	"	Depression	Broken sleep	Present	None of note	Kept on with housework	3 "	I.S.Q.
160	F	49	"	Indigestion	Nightmares	None	Could not write letters	"	2½ years	Recovered
161*	F	48	"	Bad taste in mouth	Broken sleep	Present	Lost interest in her hens	"	8 months	Improving
166	M	43	"	Fatigue	Early waking	"	Lost interest in hobbies	Off work	7 "	Recovered
167	F	42	"	Depression	Broken sleep; wakes early	"	None of note	Kept on with housework	2 "	Improving
170	F	40	In 1939 was in mental hospital	Fatigue	Broken sleep	None	Became irritable	Off work	1 year	Recovered
172	F	44	None	Dizzy bouts	Early waking	"	Weeping bouts	Work modified	4 months	Improving
176	F	48	"	Vaginal discharge	Broken sleep	Present	"	Carried on with work	1 month	I.S.Q.
178	M	37	"	Cough	Difficulty in falling to sleep	None	Gave up rabbit breeding	"	8 months	Recovered
180	M	47	"	"	Cannot sleep for cough	Present	None of note	"	10 "	I.S.Q.

* Case described more fully in text.

environment has changed he will usually admit that the change lies in himself. He is a different man from what he used to be. He has difficulty in concentrating and in thinking things out. He has to drive himself to do his work. Even his hobbies have lost all attraction. Actual retardation may be difficult to demonstrate, but the sevens test is sometimes useful. The patient is asked to subtract 7 from 100, and then 7 from 93 and so on, until he has reached the lowest possible digit, which is 2 if his calculations are correct. The usual time for a brain-worker is about 30 seconds. The test can be repeated at intervals, and an improvement in the time is some indication of progress.

To the depressive the future looks very gloomy, if not hopeless, and reassurance is not readily accepted. Delusions, such as poverty or that something dreadful is going to happen either to the patient or to one of his near relations, are not uncommon. The patient is prone to get lost in his thoughts. He may sit for ten minutes before doing a job. One patient, at her worst, could not account for a whole day, but none of her relations had noticed any gross peculiarity during that time. Vertigo or fainting is a common symptom among women.

Suicidal Ideas

This subject must be approached with tact. One does not want to upset the patient or to put ideas into his head. If he admits depression one can inquire if he feels bad enough to wish he was out of it. Most of these patients admit that they have had such wishes. One can then ask if they had had any ideas about suicide. Some will agree, and others who may show surprise will say they have never reached such a pitch of depression.

Sleep Rhythm

Few depressives get off without some upset in their normal sleep habits. The classical story is that they get off to sleep fairly easily, but that the least noise awakens them and their sleep has gone. Others wake up in the early hours and cannot get off again. It is during these early hours that they feel worst and suicide is most likely to occur. As the morning wears on they improve and by nightfall feel positively normal, only to waken early the next morning to start the same dismal rhythm again. Some few depressives enjoy good sleep. Others are afflicted with bad dreams and wake exhausted in the morning. Others have difficulty in dropping off to sleep; but such suggests an anxiety state. With some, no two nights are the same. If there is no upset in the sleep rhythm one must seriously question the diagnosis of endogenous depression.

Change in Habit and Outlook

This is often very striking. One patient mentioned that she had always been musical, but since her illness had started she could not bring herself to play the piano. An amateur comedian found himself unable to hold his audience, and so gave up his work in the concert team. One patient gave up drinking when depressed. Others go to the opposite extreme.

Case 110.—In August, 1945, this patient was admitted to a neuropsychiatric centre agitated and visually hallucinated. His tongue was red and atrophic, and knee-jerks were absent. There was a history of heavy drinking to complete the picture of delirium tremens. On intravenous nicotinic acid and aneurin he made a rapid recovery, being mentally normal in four days. His family and past history was almost completely negative. He had begun drinking heavily in the February because he could not sleep. Even a heavy dose of brandy could not keep him asleep after 4 a.m. His commanding officer and his wife were closely questioned as to the patient's habits. His wife admitted that since the February he had changed. He had lost all interest in his home and children, never doing the odd jobs about the place to which he was accustomed. He ate and slept badly. The depression appeared to have cleared up with his delirium tremens. Both the patient and his wife affirmed that he was back to normal before he was discharged in October, 1945.

It is well worth while bearing melancholia in mind when a man, previously known to be sober, suddenly starts drinking to excess for no apparent reason.

The social man may find himself shunning society. Others fear to be alone, and seek company, but feel out of it when they get there, as they have nothing to say and are so different from what they used to be.

Case 149.—This man, aged 38, first came to see me in February, 1946. He complained of stomach-ache occurring at intervals, an occasional headache, and a listless feeling. Physical examination failed to reveal any abnormality. His knee-jerks were sluggish, but it was felt that his symptoms were those of an anxiety state. During preliminary psychotherapy he admitted a morbid fear of tuberculosis, a disease which had killed his brother. He was reported to the local tuberculosis officer, who had him *x*-rayed; but no evidence of the disease was found. As he did not report back it was assumed he had been reassured, but towards the end of April his wife communicated with the surgery. She was very worried about him, as "he was a changed man." He was depressed and unhappy, and had dropped all his social activities. He was interviewed again, and it was found that he was very low, feeling that life had lost all its charm for him. Only the thought of his wife and family prevented him from taking his life. He was worried because, while he had earned good money during the war, he had saved nothing and the family ran the risk of poverty. His sleep was poor unless he took sedatives. By the middle of May he was worse, and had a bad suicidal urge. He was taken home one night in a state of depression, and stated that but for the presence of friends he would have finished it. He was persuaded to see a psychiatrist, who suggested he needed hospital treatment at once. The patient consented, but only because he knew if he did not agree he would never get away from the psychiatrist! This man, who had been a local comedian and very sociable, became solitary and schizoid. Fortunately, soon after his visit to the psychiatrist he began to improve, and by the middle of July was back at work again.

Case 161.—This woman, aged 48, said she had been ill for about a year. She complained of a nasty taste in her mouth and tight feelings round her neck. These symptoms were always most severe in the mornings. She suffered from insomnia and was given to bouts of weeping. She was prone to lose herself for ten minutes or so at a time. She had "nasty thoughts"; these usually implied impending death to herself. When her son announced his engagement she had felt happy because she knew he would not have a mother much longer. She had wished she was dead, but when first seen that feeling had passed. She always felt better in company, which she sought, but was embarrassed when people said she was not the jolly soul she used to be.

Obsessions and Phobias

These may indicate an underlying depression. Case 149 had a phobia about tuberculosis. Other patients reveal absurd consternation about some trivial mole or wart. Early in 1946 one of the local inhabitants hanged himself because of a tapeworm which had worried him for a few months. In the Army the V.D. obsession was particularly common.

Case 27.—This man, aged 34, had an obsession about V.D. For over a year, while employed in the Middle East, he had seen every available urogenital surgeon and venereologist. He had twice submitted to cystoscopy. Before returning home he reported once more to yet another camp M.O., who took pity on the patient and threatened him with "You don't want to be sent to a psychiatrist, do you?" He ended up at a neuropsychiatric centre, and was given psychotherapy as an obsessional case. He became much worse and made a strong negative transference with his therapist. When seen in March, 1945, there was no obvious cause for any anxiety. He talked too frankly about his sex life, which as Ross (1937) suggested was a pointer towards a psychosis. He had marked feelings of unworthiness, and was always comparing himself unfavourably with others. He was depressed and had suicidal ideas. He slept badly. He was given six E.C.T. treatments and rapidly lost his obsession for V.D. When seen seven months later he was back at work and apparently fully recovered.

Some innocent organ may be blamed for the patient's feelings of ill-health. A man may demand the removal of his testicles, or a woman who has had a prolapse for years suddenly begins to blame it for all her symptoms and is prepared to undergo any operation to have the offending organ removed. Such operations are obviously futile and do not touch the real problem.

On the physical side there is usually no evidence of organic disease. A moderate degree of hypertension is not uncommon. The knee-jerks, which as a rule are brisk in an anxiety state, tend to be sluggish (see Case 149). Many depressives are overlaid with a fair degree of anxiety, so that the sign is not of much significance. Depression can of course be coincident with an organic disease, which may make the diagnosis much more difficult.

Case 144.—This man, aged 62, was an invalid from chronic emphysema. He had to spend most of his time sitting in a chair

as the least exertion made him breathless. He was usually cheerful and philosophical about his complaint, but in March, 1946, he became very depressed. He kept to his own room and was solitary. He felt he was finished, and wished he was dead. He had no suicidal urge. His sleep rhythm was changed and he started waking at 3 or 4 a.m. His relations had noticed the change in him. He was given luminal at night and benzedrine in the mornings. In six weeks the depression passed and he resumed his place in the family circle, feeling "his old self again."

Diagnosis

Any organic or functional disease can be simulated by the psychotic depression, but the most difficult differentiation is in the field of the psychoneurotic illnesses.

Anxiety State

The differentiation here is most important, because the deeper therapy which is applied to the neuroses is definitely contra-indicated in the endogenous depression. Case 27 shows how deep therapy can aggravate the condition.

There are two main aids in the differential diagnosis. An anxiety state can be traced back to its origin in frustration or feelings of guilt. The endogenous depression comes "out of the blue." Secondly, the "feel" of the cases is different. A bereavement will make the normal individual depressed, but his poise should have returned to normal in two weeks. The neurotic may prolong the depressive state over weeks or months. The condition is then known as a reactive depression. It is, in fact, a depression brought on by circumstances, and, like all neuroses, is an exaggeration of normal. Furthermore, a reactive depression is motivated and serves a useful purpose. The motive lies below the level of consciousness, and the purpose may be to get sympathy from the remainder of the family. Bereavement may set in motion an endogenous depression. It might be a factor, but could not be the sole cause of the illness. Much more frequently this disease comes "out of the blue." Wringing her hands, the patient exclaims: "And I should be so happy. I have such a nice home and husband, and I am so proud of my family." The illness is not engendered by circumstances and is not motivated like an anxiety state.

The second important point in the diagnosis is the "feel" of the case. It is quite different from any other illness, and the ability to feel out cases comes from the experience of handling them. The typical depressive oozes with depression—so much so that the physician himself feels depressed. This does not often happen in the mild cases described in this paper. The kind of rapport one establishes helps in the differentiation. The neurotic who is going to respond shows an intellectual interest in his treatment. The depressive allows talk to flow over him, and only appears to be interested in going over his feelings. He is never tired of telling his story over and over again. Thus with the depressive the psychotherapy is more stereotyped and easier than with the neurotic. It consists of repeated encouragement, and while the repetition may not appear to convince the patient it does not bore him. In the anxiety state there may be a hidden fear of mental illness. The patient would be very upset if this were suggested by the therapist. The depressive accepts, without resentment, the suggestion that his illness is mental, although he will dig his heels in hard at the mention of a mental hospital. In his heart he knows the way he is heading. He is grateful for the diagnosis, perhaps because he is glad to find someone who understands and can sympathize: he is so often misunderstood.

Prognosis

The one bright spot in this gloomy illness is that the prognosis is comparatively good, especially in cases of involutional melancholia. The length of the illness varies from a matter of a few weeks to months or even years. Henderson and Gillespie (1944) suggest that when relatives press for an opinion it is best to state that the attack may last for a period of 3 to 6 months. Many cases are well in much less time, but others run a longer course—maybe of years. With E.C.T. dramatic recovery is likely to occur in anything from 50 to 70% of cases of involutional states, according to Sargant and Slater (1944). Henderson, Tod, and Daly (1943) in a review of E.C.T. suggest 46% recovery in other types of depression. High-dosage insulin sometimes works where E.C.T. has failed, especially in the depressive case with schizoid characteristics. The recovery figures do not appear startling when compared with the results in the appendicectomy operation, but they are very much better than those of older methods of treatment, and in successful cases the patient is relieved of weeks or months of suffering. With patients it is wise to take a very optimistic view of treatment, but one should give the relatives a more accurate statement as to the prognosis.

Treatment

The first step in the treatment of these cases is to establish a firm rapport. The illness may be a long one, and such a rapport may well carry the patient through the bad patches when everything else seems hopeless. So far as general practice goes, the treatment is threefold—psychotherapeutic, symptomatic, and occupational.

Psychotherapy

In his book *The Common Neuroses*, Ross (1937) devotes an excellent chapter to the treatment of the mild depressive. The therapy consists largely of reassurance, and the same ground may be gone over again and again without the patient becoming bored by repetition. He should be told that his symptoms are due to an illness which is not uncommon, and which is well understood by the therapist. "I am not really ill" is a common apology offered by a patient, and it comes as a relief to know that his feelings are the expression of an illness and not due to his own peculiarity and failings. Surprise and satisfaction are often expressed when the therapist, in his patter, is able to describe some of the patient's symptoms more clearly than the patient himself. The patient realizes that here at least is someone who understands, someone to whom he can talk without being laughed at or told to "pull himself together." The only consolation is that, if he can hang on, the illness will pass over. He must be reassured that, in spite of any feelings to the contrary, the illness is self-limiting. One cannot remove a delusion by argument, but this analogy sometimes gets home: The patient is told that his "dashboard instruments" are recording falsely, and he needs to be guided by those of his doctor and his relations until accuracy is restored. He must be told to measure his progress, not by days, but by weeks or months. Even when he is climbing out of a depression he must be warned against setbacks, which frequently occur. These may be accompanied by a strong suicidal urge. Nothing is more disappointing than to lose a patient who seems to be well on the road to recovery.

Symptomatic Treatment

Every effort should be made to promote sleep. In some cases 1–3 gr. (65–195 mg.) of phenobarbitone is adequate, but usually 7½ gr. (0.5 g.) of medinal is more effective. The latter is taken dissolved in water and flavoured with sugar and fruit juice. Benzedrine sulphate is sometimes useful in dispelling the early morning depression, and creating "pep" and energy in the patient. One or two 5-mg. tablets are usually given on waking. Another may be necessary by noon. To avoid creating insomnia at night none are administered later. Aspirin compounds may be given to relieve headaches and alkaline powders to allay dyspeptic symptoms. Stilboestrol is useful to abate menopausal symptoms, but does not in itself relieve the depression. There is no need to withhold any drug which promises to relieve discomfort merely because the pain is psychogenic, but it is more important to promote reassurance and understanding than to give any form of medicine.

Occupational Therapy

This is most important. The patient is often quite unable to do any responsible work, but to make him idle by merely putting him off work is to invite trouble. Time drags horribly with a depressive, and anything which helps him to while away an hour is useful. He should be encouraged to do things with his hands, and to be sociable with his friends. He should be discouraged from lying idly on his bed or going for walks by himself with only his own wretched thoughts for company. Perhaps more important than the negative aspect of whiling away his time is the positive side of achievement. The patient feels useless and impotent, and it is often an encouraging surprise to him to find he can do even small jobs.

Specialist Treatment

E.C.T., insulin shock, and in certain cases leucotomy require specialist attention. Few forms of treatment in the whole of medicine are more dramatic or more gratifying than E.C.T. in the depressive, especially the involutional type; and here comes the rub. Very few cases found in general practice are certifiable. The patient does not resent the mental implication of the diagnosis, but he resents strongly any idea of being sent to a mental hospital for treatment. The bait of going in as a voluntary patient, of having a special ward, is quite ineffective. If the patient is suicidal the position is most embarrassing for the doctor. To send a patient in against his will would break a useful rapport. It is maintained by some psychiatrists that E.C.T. given to a resistant patient is less effective than to one who voluntarily submits.

The G.P. is looking after a large community. If every depressive were certified and sent to a mental hospital for treatment not only would his practice diminish but he would vitiate his own work. Few neurotics and depressives would have courage to confide in a man who was liable to lock them up. In any case, in America E.C.T. is given to out-patients, and the majority of mild depressives could well be treated in that way.

It is high time that every general hospital had a neuropsychiatric wing where neurotics, depressives, and amenable psychotics could be treated without the stigma of the mental hospital to add to their misery. Such a cover has already been given to patients suffering from venereal disease, but it is denied to depressives, who are more deserving of such help. If all possible cases were treated as out-patients that would save valuable hospital beds. Calling a lunatic asylum a mental hospital is a theoretical improvement, but it has not in any way allayed the public dread of such an institution. Furthermore, any "nerve hospital," no matter what euphemism labels it, is doomed to similar unpopularity. Only by incorporating the centre into a big hospital will the stigma be avoided.

During the war psychiatry has made great strides, especially in the Armed Forces. Psychiatric facilities are urgently needed by the civilian population. It is estimated that one-third of all the cases seen in general practice are functional. Psychiatric specialist facilities are meagre in the extreme. Under the present system the vast majority of mild depressives, who are far from "insane," will have to get along as best they can with the inadequate treatment which the G.P. can offer. There will be a proportionate number of suicides, which with a better system would be avoided.

Summary

Attention is drawn to the prevalence of the endogenous depression in general practice. It is a diagnosis which is often missed.

The main symptoms, the diagnosis, and the domiciliary treatment of the condition are outlined.

The difficulty of procuring special treatment is pointed out.

An appeal is made for better psychiatric facilities in general hospitals, so that amenable patients can avoid the stigma of mental hospital treatment.

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Sir JOHN CONYBEARE'S *Textbook of Medicine* by various authors first appeared in January, 1929, and by April, 1945, had gone into seven editions and four reprintings. Now it has reached an eighth edition (E. and S. Livingstone; 30s.), and the editor's skill in managing his team is no less evident than before. Most of the sections have needed only minor touching up. F. E. Lipscomb has largely rewritten the articles on malaria, blackwater fever, bacillary dysentery, and typhus, and that on effects of heat has been rewritten and transferred to the section on tropical diseases. In the section on the endocrine system there is a new article on the menopause, and many changes have been made in those on thyrotoxicosis and diseases of the pituitary gland. Now that penicillin is more and more available, and there is a large literature about its use, the editor has added a section on the subject. There is also an appendix on aviation medicine by R. H. Winfield. This textbook has won a firm place in the esteem of students and practitioners, and the new edition will maintain its well-deserved popularity.

SO-CALLED TRIPLE-SYMPTOM COMPLEX OF BEHCET

BY

E. W. PROSSER THOMAS, M.D.

In 1937 H. Behcet described what he believed to be a hitherto unrecognized morbid entity in which grave eye disease occurs in association with peculiar ulcers of the mouth and external genitals. Later he published other articles (Behcet, 1938, 1939, 1940). The clinical picture naturally is dominated by the eye lesions, which range from conjunctivitis and corneal ulceration to hypopyon uveitis, and may lead to total blindness. The eye involvement may precede, coincide with, or follow the oral and genital manifestations. Both eyes may be affected simultaneously, but more usually only one eye is involved for a while; after a variable interval the other eye shows similar changes. The ulcers of the mouth and genitals are small and discrete, either aphtha-like or nodular and necrotic, resembling periadenitis mucosa necrotica recurrens (Sutton). Other skin lesions may also occur, such as erythema nodosum or an acneform eruption. The disease, which appears to affect men twice as often as women and to occur predominantly in the third decade of life, is essentially a relapsing one over a period of years, the symptoms at the three main sites recurring simultaneously or successively. Behcet believed the syndrome to be due to a filtrable virus.

A similar combination of symptoms had been reported earlier—for instance, by Whitwell (1934) and Nishimura (1935). Whitwell concluded that there is a relatively unexplored syndrome of ulcers in the mouth accompanied by "embolic" lesions elsewhere; the syndrome may be partial—that is, mouth lesions alone—but at any time the skin and/or the vulva may be involved; eye lesions may also occur, as in one of the cases he cited. Nishimura's case was one of acute ulcer of the vulva, with aphthoid changes of the oral mucosa and acute iritis.

Since Behcet's articles a number of other cases of the same complex have been reported (Weekers and Reginster, 1939; Bechgaard, 1940; Cavara, 1940; Franceschetti and Valerio, 1940; Mach *et al.*, 1941; and Ephraim, 1944). The last-named author questioned whether ulcus neuroticum oris et vulvae (Loblewitz), periadenitis mucosa necrotica recurrens (Sutton), and aphthosis (Neumann) do not all belong to the same group. A case recorded by T. Jensen (1941) may be quoted as an example of the syndrome.

The patient was a man aged 22. The disorder began with aphthous ulcerations of the mouth at the age of 9; the ulcerations healed spontaneously in a few weeks, then recurred. Ocular symptoms appeared at 12, lasted four or five days at first and then about three weeks, and recurred at intervals of one month. Vision decreased after each attack. Iritis, iritis and choroiditis, total atrophy of the left and partial atrophy of the right optic nerve, and hypopyon were successively diagnosed. Six years later small painful ulcerations developed from time to time on the scrotum and penis. The patient gave a positive response to intradermal tests with tuberculin, Frei antigen, and dmelcos vaccine. Non-specific reaction was therefore suspected and confirmed by positive response to 0.1 ml. of a physiological salt solution. Superficial puncture of previously sterilized skin caused the appearance of a pustule the size of a pinhead and surrounded by a red somewhat infiltrated zone having a diameter of 5 mm. The pustule disappeared in four to five days, leaving some epidermal scarring. Behcet inclusion bodies were not found in the secretion of the regular ulcerations.

A case recorded by Berlin (1944) is of especial interest because, in addition to the classical eye, mouth, and genital lesions, the central nervous system was involved. Berlin's patient, whose eye disease began three and a half years after the oral and genital signs, eventually developed headache, giddiness, and fits, which culminated in coma and death. At necropsy small multiple foci of inflammation and softening were found in the brain.

The subject has been fully reviewed recently by Curth (1946) and Katzenellenbogen (1946). Curth describes the first American case of the disease. The patient was a young man with typical recurrent hypopyon which led to the enucleation

of one eye and to blindness of the other, with recurrent genital ulceration and oral aphthae. Other symptoms were attacks of arthritis of the ankles and "fibrositis" of the back. The patient also suffered from facial acne, recurrent boils, and multiple abscesses in the axillae. There was no response to a number of different treatments, including systemic penicillin and sulphonamides. Bacteriological and other studies gave no clue to the aetiopathogenesis.

Katzenellenbogen reports three cases in male Arabs. There were recurrent aphthous ulcers in the oral mucosa and in the skin of the root of the penis and scrotum, which left scars on healing. The ulcers were associated with eye disease of the character of hypopyon iritis and with haemorrhages in the retina and vitreum. These haemorrhages, which have not been stressed by other authors, contributed most to the loss of sight in two of the cases. Other lesions noted were nodules resembling erythema nodosum on the extremities and an acneform eruption on the face, extremities, and back. Relapsing epididymitis was found in two of the cases. All cases had a peculiar sensitivity of the skin. Puncture was at all times followed by pustule formation, and any injection, of whatever material, produced focal erythema and swelling. In his cases Katzenellenbogen found no evidence to support Behcet's belief in a virus causation, and failed to discover any grounds for suspecting tuberculosis. He thought, however, that the disease had qualities reminiscent of those of herpes.

The following appears to be the first case of Behcet's syndrome as such to be reported from this country.

Case Report

A married man aged 29 came under observation at St. Mary's Hospital in June, 1940, on account of a relapsing iritis in the right eye. He was employed in a munitions factory as an inspector of shells. Previously he had worked for five years as a paint-sprayer. His father, mother, one sister, and one brother were alive and well. One sister had died of pulmonary tuberculosis. He had had scarlet fever at the age of 11. Before the onset of his eye disease his general health had been fair, but for eight years—that is from the age of 21—he had suffered from ulcers of the tongue, roof of the mouth, and inside of the cheeks. These ulcers recurred irregularly, each lesion taking three or four days to mature and about the same time to subside. They were generally painful. Some were small and superficial, resembling simple aphthae, but others formed more solid nodules which broke down centrally and left scars (cf. periadenitis mucosa necrotica recurrens, Sutton).

In September, a few months after the onset of iritis, he developed a right femoral thrombophlebitis. Except for a positive Mantoux test, full investigation in hospital proved as negative at this time as it did subsequently. Focal sepsis was suspected in the tonsils, and tonsillectomy was performed in October. The disease, however, progressed, and in December thrombosis of the inferior vena cava occurred. Meanwhile the condition of the right eye had been steadily deteriorating. By March, 1941, vision was practically *nil* and there was extensive damage involving the whole uvea. The left eye also was slightly threatened. A search for a common focus of infection for the thromboses and the iritis failed, as did that for a tuberculous focus in the chest or elsewhere. Naturally it was regarded as suspicious that his sister had died of pulmonary tuberculosis.

By July the thrombosis of the inferior vena cava was subsiding, though the patient still had slight swelling of the legs after exercise, which was controlled with elastic stockings. He had been treated with prolonged rest, which when interrupted brought on exacerbations of the iritis in the right eye. The left eye had been flaring up periodically.

In August he was again admitted to hospital, this time with nausea, constant insomnia, and severe temporal headache. The eye signs were equivocal, and a cerebral neoplasm, possibly with meningeal involvement, was suspected. Lumbar puncture showed a raised pressure (250 mm.), with a clear fluid. The cell content was normal, the chemical and bacteriological examination negative. The colloidal gold test was negative, as was the Wassermann, which had been done on the blood on a number of occasions previously. Radiography showed no evidence of an intracranial space-filling lesion. An encephalogram gave no positive result. In view of his past occupation as a paint-sprayer a lead encephalopathy was suspected, but there was no evidence of skeletal lead deposition and the lead content of the urine was 0.08 part per million (normal, 0.04-0.12). No stippled erythrocytes were seen in the blood. Apart from a haemoglobin of 76%, the blood count was within normal limits. Blood culture was sterile. General physical examination again revealed no definite abnormal signs in the central nervous system, heart, or abdomen. Large veins were now present below Poupart's ligaments and across the abdomen, carrying blood upwards, presumably a relic of the bilateral femoral thrombosis. The posterior tibial arteries were present and palpable.

Meanwhile, vision in the left eye had become suddenly worse, and the headaches had increased in severity. An extensive white exudate from the choroid was seen, suggestive of choroiditis rather than papilloedema. After another month's rest, however, the headache had lessened and vision in the left eye had improved somewhat. The superior quadrants had cleared a little, but details were still not visible. He was again discharged to the out-patient department without any aetiological diagnosis having been made.

Shortly afterwards a new set of symptoms made their appearance—namely, various skin lesions, and ulcers on the scrotum and penis. The skin lesions were of three types: (*a*) Small, solid, slightly tender papules on different parts of the body, particularly the forehead, cheeks, and legs. They were of normal skin colour or sometimes a little dusky, and came and went within ten days or so without ever breaking down. (*b*) Small patches of erythema—e.g., on the chest and arms. These were thought to be due to thrombosis of a surface vein. (*c*) Larger, more tender nodules of erythema nodosum type, particularly on the thighs, giving an appearance of inflammation. One of these lesions on the leg was excised for section and was reported as showing an acute inflammation of a vein, with thrombosis; many polymorphs were seen in the thrombus and around the vessel, the inflammatory process spreading a little distance into the surrounding tissue. No organisms were seen. Aerobic and anaerobic cultures were negative. The ulcers on the scrotum and penis recurred every two weeks or so, sometimes more than one appearing at a time. They began as small, solid, tender nodules which broke down to form a sharply punched-out ulcer with a yellowish necrotic base. They invariably left scars.

In December the patient was readmitted to hospital with intense pain in the right eye and side of the head. Excision of the eye was then performed. The headaches, however, continued, now mainly left temporal, and vision failed completely in the remaining eye. He was again admitted to hospital in May, 1942, and fully investigated. His case was now, *faute de mieux*, labelled "thrombophlebitis migrans." The bleeding time, clotting time, and platelets were normal. The blood count was: Hb, 70%; white cells, 14,100 (polymorphs 73%, lymphocytes 23%, monocytes 1%, eosinophils 2%, basophils 1%). The electrocardiogram was normal. The Mantoux reaction (1/10,000) was weakly positive. As vision had failed completely and the headache and distressing pain persisted in the left orbital region, enucleation of the left eye was carried out in June.

After-history.—The patient attended the out-patient department periodically for the next two years and was treated symptomatically. His case was reported on as follows.

"January, 1943: Since discharge from hospital gets aching pain in left hip radiating to calf. Still has red nodules, especially on thighs. No further ulcers in scrotum or mouth. Spleen and liver not palpable. B.P. 118/75. Dilated veins on abdomen, especially on left. Both posterior tibials and popliteals palpable. Left calf tender. Left ankle-jerk brisker than right. Hyperaesthesia to touch round left ankle: ? early neuritis. May, 1944: Now has pain across forehead, especially on coughing. Giddy turns and fainting attacks; no fits. Legs getting weak. No sphincter disturbance. No abnormal physical signs in central nervous system. Some occipital fibrositis. Caput medusae well marked."

Eventually the patient found the journey to London too difficult because of his blindness and air raids, and ceased attendance. It has not been possible to ascertain his subsequent history.

Ophthalmic Summary

I have to thank Mr. Frank Juler for the following note:

"The ocular condition manifested itself first in June, 1940, in the form of subacute recurring iritis of the right eye with hypopyon. After some four attacks at monthly intervals, the visual acuity was reduced to 6/24, but soon after, in December, 1940, there was a fairly sudden loss of vision, with a central scotoma due to a lesion probably in the choroid. Further congestive attacks occurred in the right eye, and perception of light in this eye was lost by October, 1941. In this month glaucoma ensued, and the right eye was removed on account of pain.

"In the meantime the left eye was also attacked by subacute iritis in October, 1940; but in February, 1941, fine vitreous haze and patches of choroidal change in the periphery were noted, with vision still 6/6. In June, 1941, this eye suddenly became defective, and vision fell to finger-counting at 1.5 metres; much vitreous opacity was present and severe headache became a marked feature. In two months the eye had cleared to 6/18, and a scotoma was present owing to a large white area in the fundus near the optic disk. In September, 1941, the left eye became suddenly worse with severe congestion and headache, and by October vision was reduced to perception of light. A recurrence of iritis with hyphaemia did not improve matters, and in May, 1942, with severe pain in the head

and congestion of the eyeball, perception of light was lost. Recurring glaucoma with pain led to excision in June, 1942.

"Histological examination of the excised eyes threw little light upon the aetiology. There was complete detachment of the retina, with gross intraocular haemorrhage, chiefly subretinal. Marked patchy thickenings of the ciliary body and choroid were evident, showing reactionary changes, but there was no certain evidence that vascular thrombosis was the initial factor."

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Medical Memoranda

Intravenous Anaesthesia and Circulation Time

In all the better-known techniques for the induction of anaesthesia by the intravenous route a safety pause of 20 to 60 seconds is recommended. It is generally stated that this interval must be allowed in order to observe the effect of the drug on the patient. It seems to me more likely that its function is to permit the blood stream to transfer the drug from the site of injection to the brain. The following investigation was carried out in order to obtain more accurate information on the matter.

Investigation

Thirty-two patients were given, by intravenous injection at the elbow, 3 ml. each of a 10% solution of hexobarbitone or of a 5% solution of pentothal (thiopentone, *B.P.*). In all cases this was enough to make the patient go to sleep. The duration of the period of injection (A) and the interval from beginning the administration until the patient ceased speaking (B) were measured. It was assumed that half-way through the injection period a sleeping dose for an average patient had been given. The mean interval between the administration of this amount of drug and its action was thus obtained (Table I). It was

TABLE I.—*Mean Interval between Administration and Action of Drugs*

Drug	No. of Cases Studied	Mean Injection Time (A)	Mean Interval until Onset of Sleep (B)	$B-\frac{A}{2}$
Hexobarbitone ..	12	7·5 secs.	19·2 secs.	15·5 secs.
Pentothal	20	8·0 ,,	20·0 ,,	16·0 ,,

identical for hexobarbitone and pentothal. Further, it approximated to the arm–tongue, arm–carotid sinus, and arm–arm circulation times determined by the ordinary methods (Table II).

TABLE II.—*Circulation Time determined by Ordinary Methods*

Author	Circuit Studied	Circulation Time	Agent Used
Gargill (1933)	Arm–tongue	15·9 secs.	Sodium dehydrocholate
	Jugular vein–tongue	13·2 ,,	
Fishberg *et al.* (1933) ..	Arm–tongue	12·0 ,,	Saccharin
Blumgart and Weiss (1927a)	Arm–arm	18·0 ,,	Radioactive material
Robb and Weiss (1933)	Arm–carotid sinus	15·6 ,,	Sodium cyanide

The corresponding interval was determined in four cases for drugs injected into the internal saphenous vein at the ankle. It was found to be 35, 45, 45, and 55 seconds. Presumably the greater delay was due to the longer course which the drug traversed on its way to the heart.

The interval which occurs between the injection of an effective dose of an intravenous anaesthetic and the appearance of its action is therefore entirely traceable to the time required for its transfer from the site of injection to the brain. In normal individuals a matter of 15 seconds will suffice for drugs injected at the elbow or into the external jugular vein. As much as 60 seconds may be necessary when the veins of the foot and ankle are used. The normal circulation time is seriously prolonged in patients suffering from myocardial failure (Table III). Therefore, in the presence of any form

TABLE III.—*Circulation Time in Heart Disease*

Author	Circuit Studied	Circulation Time	Pathological Condition
Blumgart and Weiss (1927c)	Arm–arm	22–51 secs.	Arteriosclerosis and myocardial degeneration
Blumgart and Weiss (1927b)	,,	30–55 ,,	Auricular fibrillation
		15–71 ,,	Rheumatic heart disease
		17–48 ,,	Syphilitic aortitis
Gargill (1933) ..	Arm–tongue	20–52 ,,	Congestive heart failure

of serious cardiac disease great caution must be observed in the giving of intravenous anaesthetics. Methods which employ fixed rates of injection offer no protection against accident in such cases. The only safe procedure is to inject an initial small sleeping dose and observe what time elapses before its effects are apparent. A similar interval must be allowed for the appearance of the action of subsequent doses.

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Landry's Paralysis

The following case of Landry's paralysis is thought to be worth recording because of the rarity of the condition.

CASE HISTORY

A man aged 26 was admitted to hospital complaining of weakness of the arms and legs. He had been demobilized from the Navy six months previously and had been quite well until ten days before admission, when he had had a short bout of vomiting and diarrhoea. Three days before admission he developed "pins and needles" in his fingers, and his hands felt weak. Next day he could not move his fingers at all, and his feet alternately burned and felt cold and numb. By the third day he was unable to stand because of weakness of the legs.

On admission, on the fourth day, he had a complete flaccid paralysis of the muscles of the hands and forearms and of the triceps and deltoids. All the other muscles of the limbs and trunk showed extreme weakness bordering on paralysis. All reflexes except the cremasterics were absent. There was also aphonia and retention of urine. The bowels had not been opened for two days. The muscles of the head and neck were normal. There was slight blunting of sensation on the hands and feet; otherwise sensation was unaffected. The temperature was 99.2° F. (37.3° C.) on admission, but never exceeded 98.4° F. (36.9° C.) during the remainder of his stay in hospital. There were no other symptoms or abnormal findings. Examination of the cerebrospinal fluid showed: pressure and appearance normal; total protein 0.140%; other constituents normal; W. R. and Lange's test negative. The blood contained 14,000 white cells per c.mm. (85% polymorphs), and the W. R. was negative. *X*-ray examination of skull and cervical spine revealed nothing abnormal.

On the fifth day the patient regained control of his bladder, and the bowels functioned normally after the administration of an enema. The paralysis continued to extend, however, and reached its height on the seventh day. At this stage there was aphonia, slight dysphagia, and flaccid paralysis of the whole body except the diaphragm and the muscles of head and neck. The cremasteric was the only reflex which could be demonstrated.

On the same day the first signs of recovery were noticed—his ability to make slight movements of the fingers. By the ninth day the fingers moved well and the arms could be flexed. By the twelfth day the voice was noticeably stronger, one leg and both arms moved well, and there was at least a little power in all the affected muscles. The knee-jerks and plantar responses returned on the eighteenth day, and all the other reflexes during the following week. The patient was discharged, completely recovered, five weeks from the onset of paralysis.

I am indebted to Dr. W. H. James, medical superintendent of the Beverley Emergency Hospital, for permission to publish this case.

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Reviews

DISEASES OF THE ADRENALS

Diseases of the Adrenals. By Louis J. Soffer, M.D. (Pp. 304; illustrated with 42 engravings and two coloured plates. 28s.) London: Henry Kimpton. 1946.

Although diseases of the adrenal glands are uncommon, they are of profound interest because of their far-reaching effects on the mental and physical well-being of the patient. Dr. Soffer is well qualified to describe them, for he has had considerable experience of clinical practice and experimental research in this field. His book begins with an account of the anatomy and embryology of the adrenals and a useful summary of the chemical and other special investigations used in the diagnosis of adrenal disease; an account is then given of the physiology of the adrenals. The number of steroid hormones isolated from adrenal cortical extract at present totals 25, and it is expected that more fractions will be isolated in the future; there is presumably some form of mutual balance or synergy between them. This is illustrated by the fact that the whole extract will not produce hypertension, and desoxycorticosterone will not produce hypertension if the adrenals are intact but will do so in patients with adrenal insufficiency.

Cortical extracts have been used in various forms of shock during the war, but on the whole the results have been disappointing. Addison's disease is described in detail, and Dr. Soffer shows that with modern measures a third of his patients are alive four to seven years after the institution of treatment. There follows a fascinating study of the adrenogenital syndrome. The active male sexual life of many female pseudo-hermaphrodites and the psychical changes in Cushing's syndrome are remarkable biological phenomena: not only are they of importance for psycho-sexual theories, but they are of great practical concern, for the incidence of pseudo-hermaphrodites is approximately 1 in 1,000 people. Finally there is an account of the tumours of the adrenal medulla. Dr. Soffer handles his subject and its copious literature with complete control, his style is clear and readable, and he has done full justice to the subject in fewer than 300 pages. His monograph is well printed and illustrated; it is greatly to be commended.

GROUNDWORK OF PHYSICAL TRAINING

Principles of Anatomy and Physiology for Physical Training Instructors in the Royal Air Force. (Pp. 180; 158 figures. 7s. 6d.) London: H.M. Stationery Office. 1946.

This small and attractive book, authorized by the Air Council and introduced by a foreword written by the late Director-General Sir Harold Whittingham, has many things to commend it not only to physical training instructors, for whom it is written, but to many general practitioners. "P.T.I.s" cannot fail to have their enthusiasm and interest captured by the simplicity and clarity of presentation, by the attractive illustrations and diagrams, and the "comfortable" style of simple English in which it is written. "G.P.s" who are not too proud but are ready to admit rustiness in their anatomy and physiology will find this book a most attractive means of refreshing their knowledge with a minimum of trouble. But one word of warning: the example of a day's diet on page 105 must have been the work either of someone living in the past or with foreknowledge of the early lifting of food rationing. Here it is stated that "The calorie requirements of a man doing light manual work are shown below, expressed as a specimen diet for twenty-four hours." Do those who come under R.A.F. physical training instruction really have porridge, bacon (2 oz.), egg, sugar, marmalade, butter, and white bread for breakfast? Is this a subtle way of letting us into State secrets, and are we entitled to drink their health in the pint of milk that appears later in the diet? But apart from this at the moment obviously unpractical example the physiological section is extremely well presented.

The chapter on medical rehabilitation in the R.A.F. makes fascinating reading. Every consultant, practitioner, physiotherapist, as well as P.T. instructor, who studies this book will be a gainer and will certainly improve his understanding of the science of rehabilitation.

INDUSTRIAL TOXICOLOGY

Industrial Toxicology. By Alice Hamilton, M.D., and Rutherford T. Johnstone, M.D. Edited by Henry A. Christian, M.D., Sc.D. (Pp. 125. 15s.) New York and London: Oxford University Press. 1946.

This book is a reprint of a section of the Oxford Loose Leaf Medicine and has the same page numbers as in that work. Industrial medicine is an artificial grouping of different sections of medicine which have an application in industry. These include physiology, psychology, heating, ventilation, statistics, skin diseases, accident surgery, ophthalmic medicine and surgery, industrial pulmonary disease, and industrial toxicology. These subjects are so diverse that a man may cover them in a form of general practice but no individual can possibly be an expert in every branch. The subject of industrial toxicology, the knowledge of injurious actions of substances used in industry, has always been important; it is perhaps the most important branch of industrial medicine, so much so that the two have often been regarded as synonymous. Its importance has rapidly increased during recent years with the flood of new and complex chemicals which find their way into industry for diverse purposes. One cannot therefore but welcome a new book on toxicology from the United States, even though the principal criticism of the book is that, though published in 1945, it has not appeared in this country until August, 1946, and it conspicuously does not refer to much of the newest work on the subject such as manganese pneumonia, the latest reported cases of beryllium poisoning, and tri-ortho-cresyl phosphate. Nevertheless it is a full book, well written and well documented.

Many doctors are now faced with the problems of the diagnosis and treatment of injuries and diseases developing in workers by reason of conditions associated with their work; this applies not only to the industrial medical officer and general practitioner but to every physician who may be consulted by a worker. This book should therefore appeal to a very wide field and we can with confidence commend it to all of them.

CATALAN CULTURE

The Spirit of Catalonia. By J. Trueta. (Pp. 198. 8s. 6d.) London: Oxford University Press. 1946.

The rise and fall of the Catalan culture on the eastern seaboard of the Iberian Peninsula and in the south of France is less well known in England than its peculiar interest merits. From the tolerant, humane, inquiring spirit of thirteenth-century Catalonians was created the first democratic government in the world: all society was represented—ecclesiastics, noblemen, villagers—and no law could be passed without the approval of their representatives, a state of affairs epitomized by Lullius writing at about that time: "Men are serfs of other men, but their ownership, my Lord, is not essential but accidental."

This concise and scholarly book by the eminent Catalan surgeon is as crowded as an illuminated missal with portraits of Catalonia's famous men—Lullius, Arnau de Vilanova, Sibiude, Vives, Servetus (the first to suggest the blood's circulation)—and though the style is marred at times by a flatness inappropriate to the exposition of a people's spirit, the matter is well worth the general reader's attention. There are still lessons to be learnt from Arnau de Vilanova, author of many medical treatises, accusing the teachers "of losing themselves in universals and ignoring particulars, as well as of their unfounded therapeutical empiricism, which lost itself in particulars and ignored general principles"; and from Sibiude's neatly incised bridge between scholasticism and humanism: "Man is the limited reproduction of the Creator, and thus a scientific knowledge of man may bring us by successive steps to the knowledge of God."

The history of a people such as this, blessed at its birth with the poetry of Provence, tempered by conflict with the Moors, rising to great maritime power and summits of philosophical thought, only to sink back into oblivion, poses, as we have suggested, a problem of particular interest to us: what is the nature of that cultural force which, suddenly liberated, waxes so imperiously and as inexorably declines? The accidentals of the course are well described by Dr. Trueta—the policy of Ferdinand (Machiavelli's *The Prince*), the Inquisition, the alien military coups. The essence remains as inscrutable as the curve of an individual life.

PHARMACEUTICAL ASPECTS OF PENICILLIN

Penicillin: Its Properties, Uses and Preparations. (Pp. 199; illustrated. 10s. 6d.) London: The Pharmaceutical Press. 1946.

Penicillin: Its Properties, Uses and Preparations is published by direction of the Council of the Pharmaceutical Society of Great Britain, and its authorship is undisclosed. Said to have been inspired originally by a stream of inquiries coming to the editor of the *Pharmaceutical Journal*, it has been expanded into a scholarly treatise which will be found a useful work of reference. It concludes with a bibliography of 331 items. This book has evidently been written chiefly for the benefit of the pharmacist, and deals exhaustively with the aspects that concern him most. There is a whole chapter devoted to the question of stability, and the account of penicillin preparations is one of the most complete yet to appear, many alternative formulae being given. The account of clinical uses, though occupying only a single chapter of 34 pages, is adequate as an outline of the scope of penicillin treatment and of the general lines which it should follow. In this chapter it is repeatedly suggested that a dose of 200,000 units or more given twice daily is adequate for many purposes. This is a wasteful if convenient system, and evidence that its effect equals that of much smaller doses given frequently is not yet forthcoming.

There is a somewhat resentful reference in the preface to the suggestion made in the earliest days of treatment with penicillin that its dispensing should be undertaken "by bacteriologists rather than by those trained in such work." No one would wish to maintain this attitude to-day, but let it not be forgotten that a good aseptic technique is still necessary: it is admitted on page 115 that some pharmacies are structurally unsuitable for aseptic dispensing. There is a tendency in other directions to reverse the policy of 1943; it is emphasized that some preparations need not be sterile, that economy is no longer necessary, and that bacteriological diagnosis is superfluous. These encouragements to lavish use may be justified by the present supply position, and such use there will certainly be, whether encouraged in print or not. We nevertheless find it rather shocking that it should be thought necessary to say: "It would be wise, in order that this most useful substance should not become discredited, to resist the lay suggestion, which sometimes amounts to a demand, that no person should be allowed to die without having been given penicillin."

The Distressed Mind, by J. A. C. BROWN, is published as No. 115 of The Thinker's Library, by Watts and Co. at 2s. 6d. This is a digest of psychiatry and a very readable, comprehensive and clearly expressed one. To the reader already versed in psychology, psychopathology, and psychiatry it all seems delightfully simple. Even the doctrines of Freud, Jung, and Adler are set out in simple terms. The danger of such digests lies in their own virtues of simplicity and clarity, for the uninstructed reader is apt to think that the whole subject is simple and easy. In justice to the author, however, it should be pointed out that he does not say so, and that the difficulties and complexities are stressed. The chapter on psychopathic states is excellent, pointing out as it does how many criminals belong to this class and how difficult it is to treat since there is almost certainly a constitutional factor in their genesis. It is as well that the public should realize that while psychiatry has an important part to play in the understanding and prevention of crime its role in the direct treatment of the criminal may be limited. In his chapter on treatment the author is wise in that he gives some detail with regard to physical forms of therapy which the general public cannot apply, but little detail of psychotherapy which the general public would like to apply. This little book, in view of its brevity, clarity, and low price, will doubtless appeal to a large public, and it can certainly be recommended if such simplifications of a complex subject are to be recommended at all.

H. E. Cox's *Chemical Analysis of Foods* (J. and A. Churchill; 24s.) now appears in a third edition. It is not much enlarged but contains a considerable amount of new matter replacing some which though not obsolete is sufficiently available in former editions. This is a result of the exigencies of the present period. The new material, however, includes all the subjects that have come into prominence during the past few years, and this brings the volume up to date in the matter of vitamins and the newer official regulations governing the sale of foods. It is a most useful book to those engaged in the analytical examination of foods.

BOOKS RECEIVED

[*Review is not precluded by notice here of books recently received*]

1946 Year Book of Radiology. Edited by C. A. Waters, M.D., and I. I. Kaplan, M.D. (Pp. 464. $5.50.) Chicago: The Year Book Publishers, Inc. 1946.

The book is in two parts: diagnosis and therapeutics. Includes articles on tracer chemistry, pneumography of the knee, tomography of the gall-bladder, stereoscopic fluoroscopy, varieties of lobar and segmental collapse of lung, and many others.

New Aspects of John and William Hunter. By Jane M. Oppenheimer. (Pp. 188. 25s.) London: W. Heinemann. 1946.

An American biography of the famous surgeon and his brother.

Your Guide to the National Health Service. By A. D. Le Vay, M.S., F.R.C.S. (Pp. 78. 3s 6d.) London: Hamish Hamilton. 1946.

An exposition and interpretation of the Act, a survey of past and present health services, and an account of the effects of the Act on doctors and ancillary medical services.

The Household Doctor. Anonymous. Revised. (Pp. 224. 3s. 6d.) London: English Universities Press. 1946.

A popular book whose first object is to teach the principles of healthy living. The treatment of many minor and some major diseases is also dealt with from the practical point of view.

The Use of Research by Professional Associations in Determining Program and Policy. By Esther L. Brown. (Pp. 39. 25 c.) New York: Russell Sage Foundation. 1946.

The utilization of research and scientific techniques by professional associations in America, with particular reference to the American Library Association.

Neue Wege in der Diagnostik und Therapie der Lues. By A. Rottmann. (Pp. 128. No price.) Vienna: Brüder Hollinek. 1946.

Summarizes the author's experience in the diagnosis of syphilis.

Surgical Clinics of North America, October, 1946. By various contributors. (Pp. 268. Year's subscription for 6 numbers: cloth covers, 75s.; paper, 55s.) Philadelphia and London: W. B. Saunders. 1946.

Contains three symposia: (1) Aseptic surgical technique and its application to thoracic surgery, from Duke University. (2) Gastro-intestinal surgery, from Cincinnati University. (3) Genito-urinary surgery, from Tulane University and the Ochsner Clinic.

The Nature of Disease up to Date. By J. E. R. McDonagh, F.R.C.S. (Pp. 168. 15s.) W. Heinemann. 1946.

The author develops a theory on the composition and "pulsation" of proteins and their relationship to life and disease in the soil, plants, animals, and man, with particular reference to the blood proteins.

Shall We Live or Die? By Robert Morton. (Pp. 114. 7s. 6d.) St. Botolph Publishing Co. 1946.

A survey of the apparent decline in Western culture and its causes. Suggested cures include harder living in the open air, fresh food, non-industrialized agriculture, and the reinstatement of faith in living.

Clinical Methods of Neuro-ophthalmologic Examination. By A. Kestenbaum, M.D. (Pp. 384. $6.75.) New York: Grune and Stratton. 1946.

A review of the clinical methods of ophthalmological examination used in the differential diagnosis of nervous diseases, by the Assistant Clinical Professor of Ophthalmology, New York University. Diseases that affect the eye and the C.N.S. in a parallel way are not considered.

Intracranial Complications of Ear, Nose, and Throat Infections. By H. Brunner, M.D. (Pp. 444. No price.) Chicago: The Year Book Publishers. 1946.

An account of a quarter of a century's work in this field by the Associate Professor of Otolaryngology at Illinois University. Not intended as a textbook; the reader is presumed to be acquainted with the principles of otorhinology.

Essai d'Exploration Humaine. By J. F. Portié. (Pp. 408. No price.) Paris: Presses Universitaires de France. 1947.

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RETIREMENT OF THE EDITOR

The issue of the *Journal* of Dec. 28 was the last to go to press under the editorship of Dr. Norman Gerald Horner, who retired on Dec. 31 on reaching the age limit for his office. He was appointed Editor by the Council of the British Medical Association in January, 1928, when he succeeded his distinguished predecessor, Sir Dawson Williams, to whom he had acted as Assistant since 1917, after serving as a Captain in the R.A.M.C. in the war of 1914–18. Before that Dr. Horner had been on the staff of the *Lancet*, which he joined in 1911 at the time of the National Health Insurance Act; his retirement from the *B.M.J.* coincides with the passing of Mr. Bevan's National Health Service Act.

During his 19 years of editorship of the *Journal* he has seen the B.M.A. reach out for new conceptions of a medical service, formulated before the recent war in the revised Report on a General Medical Service for the Nation, published in 1938, and the Draft Interim Report of the Medical Planning Commission, published in 1942. During his hard-working years as a medical journalist Dr. Horner has witnessed not only two revolutions in medical service—troubled times indeed—but also revolutionary changes in medical science. It is hard to believe that in 1911 Hopkins had not yet published his epoch-making article on accessory food factors, and that the word "vitamine" had in that year been introduced by Casimir Funk. Insulin was discovered in 1921, and since then the science of endocrinology may be said to have grown into full adult stature. The past 10 years have seen the conquest of disease advanced an important stage further by the discoveries of the new chemotherapy. The pace of research has been breathless, and we can do no more than mention one or two milestones in medical progress, not forgetting the fearlessness and skill of the surgeon in exploring the cavities of the body, and the development of thoracic surgery and neurosurgery as compact specialties.

The rapid evolution of medicine in all its phases during the period covered by two world wars has placed a heavy responsibility upon the Editor of the *Journal*, which has not only had to serve as a scientific weekly newspaper but has also had to expound and interpret the policy of the British Medical Association. To preside over the destinies of the *Journal* during this time has been a difficult task, and one not made easier by the war of 1939–45, when the editing continued to be done in London and two changes of printer ensued on the destruction of the *Journal*'s printers by enemy action in May, 1941. That Dr. Horner has maintained the tradition and enhanced the reputation of the *British Medical Journal* in this and in other countries has been shown among other things by its steadily growing circulation. His services to medicine have been recognized by honorary election to Fellowships of the Royal College of Physicians and the Royal College of Surgeons. He leaves behind him a record of painstaking and conscientious work, a name for scrupulous fairness in controversy, and a reputation for a felicitous pen. His successor inherits a tradition of faithful service.

PROTEIN REQUIREMENTS OF ADULTS

The protein requirement of adults has been the subject of research from time to time, and speculation has sometimes been based on insufficient evidence. The difficulty is that though long-term balance studies are necessary the very conditions of such an experiment, involving as it does a constancy of diet over long periods of time, may lead to an abnormal situation. Hegsted, Tsongas, Abbott, and Stare[1] recently studied the nitrogen balance in twenty-six apparently healthy adult subjects aged 19 to 50 years who were fed on diets low in protein and devoid of animal protein; and they investigated the effect of replacing part of the protein in the diet by meat, soy flour, wheat germ, and white bread. They regard it as essential that in evaluating the nutritional value of the proteins in a diet by nitrogen-balance studies the level of protein given should be sufficiently low to produce a negative nitrogen balance, and that the diet should be fed for long enough to assure a reasonably constant nitrogen output. Owing to the lag in the change of nitrogen excretion with decreases in dietary nitrogen, short periods will show negative balances that are too large. Thus if either of these two conditions is not met the determined requirement for nitrogen will be too high.

Leitch and Duckworth,[2] from a study of published data on nitrogen balances with varying levels of protein intake, estimated the average human requirement to be approximately 50 g. per day. By what appears to have been a more rigorous selection of metabolic data Sherman and his colleagues[3] estimated the requirement to be about 44 g. per day for a 70-kg. man. Nevertheless many of the data used by the latter investigators were collected from subjects on diets consisting almost wholly of a single protein-containing food, so the estimate may be unduly high, since in a more mixed diet the supplemental effect of the proteins would more readily make up the amino-acid requirements of the organism.

Another method of approach to this problem is based on the general finding that there is a parallelism between basal energy metabolism and endogenous nitrogen excretion (Brody,[4] Terroine,[5] Sorg-Matter,[6] Smuts[7]) in all species from mice to dairy cows. This is approximately 2 mg. nitrogen (12.5 mg. protein) per calorie of basal heat expended. Terroine[8] pointed out that if we assume that this minimum protein requirement is replaceable gramme for gramme by a completely digestible protein with a bio-

1 *J. Lab. clin. Med.*, 1946, **31**, 261.
2 *Nutr. Abstr. Rev.*, 1937, **7**, 257.
3 *J. biol. Chem.*, 1920, **41**, 97.
4 *Bioenergetics and Growth*, New York, 1945.
5 *Arch. internat. Physiol.*, 1928, **30**, 115.
6 Ibid., 1928, **30**, 126.
7 *J. Nutrit.*, 1935, **9**, 403.
8 *Quart. Bull. Hlth. Org. L.o.N.*, 1936, **5**, 427.

logical value of 100, then the adult human requirement is of the order of 19 g.; or if a protein or proteins with a biological value as low as 50 are used, then the requirement is approximately 38 g. Incomplete digestion would of course raise the requirement. On this theoretical basis the requirement of man is of the order of 20–40 g. protein per day.

In the study by Hegsted and his fellow-workers the basic diet was selected to approximate in some respects to certain low-cost diets and was devoid of animal protein. White bread supplied 50% of the nitrogen; a total of 62% was supplied by cereals. Potatoes supplied 13%, and the total from vegetables was approximately 30%. The remaining 8% came from fruits. The protein intake was kept constant. The remainder of the diet consisted of butter, cooking oils, corn-starch biscuits, jelly, syrup, sugar, and sweets. The subjects were allowed these fat and carbohydrate foods freely, but everything was recorded. When meat was being tested the intake of the foods containing vegetable protein was decreased by one-third, and sufficient meat was added to supply approximately the nitrogen thus removed. The loss in calories was made good by additional amounts of the calorie supplements. The same procedure was adopted when testing soy flour and wheat germ; the vitamin and mineral contents of the diets were maintained by supplements. Certain other variations in the diets were also investigated. The authors of this investigation appreciated that owing to the shortness of the preparatory period some of their subjects were not stabilized accurately. They believe that this has the effect of placing the protein requirement at a somewhat high level.

The data from these experiments were analysed on the basis of the estimated intake at the point of nitrogen equilibrium. The daily requirement for maintaining nitrogen balance on a vegetable protein diet was approximately 2.9 g. nitrogen (18 g. protein) per square metre body surface—equivalent to 30–40 g. protein—depending on height. When meat replaced one-third of the vegetable protein the protein requirement was found to be 17% less. The biological value of the low-protein (all-vegetable) diet used in these studies was increased from 72.5 to 80.4 by replacing one-third of the protein by meat. Those who have had considerable experience of nitrogen-metabolism studies are well aware of the very considerable day-to-day variations in urinary nitrogen excretion which can take place in some apparently normal individuals, variations not due to inaccuracies but to some instability in protein metabolism. Further considerably longer periods of collection are necessary if error resulting from the ill-defined spread of the usual time-markers for faecal collections is to be offset. Cuthbertson and Munro[9] have also demonstrated the effect on nitrogen equilibrium of non-protein food consumed in excess of calorie requirement. Some caution is therefore to be exercised in interpreting the data of this recent work by Hegsted and his colleagues.

These requirements for protein are not to be confused with protein allowances. The latter are generally assessed as 50% greater than actual requirement so as to allow for safety. In accordance with Sherman's assessment the League of Nations placed their allowance for men at 1 g. protein per kg. body weight. Determinations of the protein intake in the diets of most peoples in temperate climates indicate that the level of these nutrients tends to be fixed at roughly 10–14% of the total calories, which for normal expenditure levels is approximately the equivalent of the League of Nations allowance. It is probable that the difference between normal dietary practice and requirement is also dictated by the fact that most members of the family tend to take out of the "common pot" that measure of food which is appropriate to their energy requirements. Although school milk schemes and the distribution of milk and vitamin concentrates to priority classes are tending to alter this, the design of human diets still appears to be adapted to meet the divergent needs of the various members of the family.

[9] *Biochem. J.*, 1937, **31**, 694.

CANCER CELLS IN SPUTUM

Although the technique of thoracic surgery has been highly perfected, Tudor Edwards[1] found that he was able to perform a pneumonectomy in only 66 out of 1,016 cases of bronchial carcinoma which he had seen. The importance of methods for the early diagnosis of the condition is more than apparent. Present methods of diagnosis consist of a consideration of physical signs, symptoms, skiagrams, bronchographic and bronchoscopic investigation with histological examination of the sections obtained, direct aspiration of the tumour through the chest wall, and thoracotomy. Little attention has been paid to the simple procedure of microscopical examination of the sputum.

As early as 1860 Beale[2] described masses of malignant cells in the sputum from a case of advanced pharyngeal carcinoma; Betschart[3] in 1895 described four cases of malignant disease of the lung in which pieces of tumour were expectorated; and in 1913 Weller,[4] in an analysis of ninety cases of primary bronchial carcinoma, stated that malignant cells had been found in the sputum from four cases. Nevertheless this form of investigation was not properly developed until Dudgeon and Wrigley[5] in 1935 published a detailed account of a wet-film method for the examination of the sputum for evidence of malignant growth. Since then considerable success has been reported in many countries—70% in Russia,[6] 86% in Denmark[7]—and enthusiastic reports have been published in Latin America.[8]

In England first Dudgeon,[9] then Barrett,[10] and then Bamforth[11] reported the results from St. Thomas's Hospital. In the first paper an account was given of 102 cases examined, of which fifty-six were eventually proved to be cases of malignant disease; out of the fifty-six a total of forty-three, or 76%, were diagnosed by examination of sputum. The second paper added 119 positive cases, and the third a further 113. Sambrook Gowar[12] used the method in ninety-three cases of proved or probable carcinoma at the London Hospital and obtained a positive result in 64.3%. He drew attention to the fact that a high proportion of the positive cases were of the squamous cell

[1] *Thorax*, 1946, **1**, 1.
[2] *Arch. Med. Lond.*, 1860, **2**, 44.
[3] *Virchows Arch.*, 1895, **142**, 86.
[4] *Arch. intern. Med.*, 1913, **11**, 314.
[5] *J. Laryng.*, 1935, **50**, 752.
[6] Altgauzen, A. Y., *Klin. Med.*, 1939, **17**, 90.
[7] Wandall, H. H., *Acta path. microbiol. scand.*, 1943, **20**, 485.
[8] Nosto, D., Polak, M., *Sem. méd. B. Aires*, 1937, **44**, 1549; Bence, A. E., *Ibid.*, 1940, **47**, 836; Izzo, R. A., Irigoyen, L., *Publ. Centro Invest. fisiol.*, 1943, **7**, 323.
[9] *St. Thom. Hosp. Rep.*, 1936, **1**, 51.
[10] *J. Thorac. Surg.*, 1938, **8**, 169.
[11] *Thorax*, 1946, **1**, 118.
[12] *Brit. J. Surg.*, 1942, **30**, 193.

type, though these probably only form a third of the cases of carcinoma of bronchus. Gloyne,[13] in a paper on the cytology of sputum, also commented on the greater frequency with which squamous-cell growths were detected in the sputum and suggested that it was due to early breaking down of these growths, whereas oat-cell carcinomata do not ulcerate till a late stage and do not readily break down.

This year also a report has come from Herbut and Clerf[14] in Philadelphia on the examination of bronchial secretion for malignant cells. They chose bronchial secretions rather than sputum because they consider that they are more concentrated, and that expectoration of sputum does not occur until late in the disease. Bronchoscopy is now performed as a routine in every case of suspected pulmonary cancer; and material which comes from the area of the suspected tumour is more likely to contain cancer cells than are the more dilute secretions found in the trachea and the even more dilute sputum. They claim that in thirty consecutive cases of primary pulmonary carcinoma cancer cells were demonstrated in the bronchial secretions of twenty-two, or 73%. Bronchoscopy was negative in seven of these cases. Sputum was examined from five cases in which cancer cells were present in the bronchial secretions and in only one were neoplastic cells found.

Bamforth, in his article[11] in *Thorax*, reported also that a number of specimens of pleural fluid were examined between December, 1937, and March, 1946, and that in thirty-one cases a positive diagnosis was made by examination of the pleural fluid. In thirteen cases considered to be primary carcinomata of the lung no evidence of neoplasm was found outside the chest. Obviously a case with a pleural effusion is inoperable, but it is frequently difficult to establish the diagnosis with certainty; a simple method which can achieve this would be of the greatest practical value.

PLEURAL GAS ANALYSIS

Analysis of the pleural gases in cases of pneumothorax often yields useful information, and the pioneer work of Coryllos has done much to show the possibilities of this method, particularly in the clinical diagnosis of bronchial fistulae. A recent paper by Ornstein, Herman, and Friedman[15] serves to emphasize some of the many problems connected with the behaviour of the pleural gases which still remain unsolved. These authors consider that in the past too little attention has been paid to the role of the pleura in affecting gaseous exchanges, and they challenge the diffusion theory which most physiologists have advanced to account for the absorption of gases from the pleural cavity. According to this theory the oxygen and carbon dioxide in the pleural cavity reach equilibrium with the corresponding gases in the venous blood, thereby raising the partial pressure of the pleural nitrogen above that in the capillaries. The nitrogen therefore diffuses out of the pleural cavity and thus raises the partial pressures of the pleural oxygen and carbon dioxide above those in the venous blood. The cycle then repeats itself until all the gases are absorbed.

In a large series of observations Ornstein, Herman, and Friedman found wide variations in the oxygen and carbon dioxide content of the pleural gases in different cases, although the values were usually constant for the same individual. Moreover, the partial pressures of these gases were often different from the theoretical pressures of the corresponding gases in the venous blood. The authors conclude that the pleural oxygen is not in equilibrium with that in the venous blood. They also found that the volume per cent. of carbon dioxide in the pleural cavity was remarkably constant in individual cases, whereas the diffusion theory suggests that the level should vary at different times after a refill. They infer that the pleural gases are in equilibrium with the pleural tissues rather than with the venous blood, and that oxidative processes in the pleura are responsible for the high carbon dioxide and low oxygen values so often encountered, and for the outpouring of carbon dioxide after pleural lavage with oxygen. The absorption of nitrogen still remains to be explained, and they suggest that the expanding lung may exert sufficient pressure on the pleural gases to raise the partial pressure of the nitrogen to a level which will ensure its absorption.

There are many weak links in this chain of reasoning. The fallacies of theoretical estimation of the gases in the venous blood are well known, and we have no means of determining the values for the pleural circulation. Again, the pleura itself may act as a variable resistance and under certain conditions, such as pleurisy, may impede the passage of gases to and from its capillaries. Finally, there is no evidence that the expanding lung exerts any pressure on the pleural gases. However, this paper serves a useful purpose in drawing attention to these problems of the pleura and to the possibilities for further research based on gas analyses.

Another observation reported by these investigators will interest many tuberculosis workers. In five cases they measured the volume of the pleural cavity twenty-four hours after the induction of a pneumothorax, and in every case the volume was greater than that of the air injected. They conclude that the excess air must have escaped from a puncture in the lung. Tchertkoff[16] propounded the theory that the lung was always punctured during the induction of a pneumothorax and that the initial pleural space was produced in this way. Most workers believe that a blunt cannula can be introduced between the pleural layers without puncturing the lung, but this requires investigation. It should be relatively simple to find out by pleural volume estimations how often the lung is punctured when using different induction techniques. Such information would have an important bearing upon the design of pneumothorax needles.

MYOCARDITIS IN MUMPS

Cardiac injury is not usually regarded as a common complication of mumps. As with any other acute infection convalescence is sometimes retarded by the presence of slight cardiac dilatation, with perhaps a soft systolic murmur at the apex which would usually be regarded as non-specific in origin. Apart from Pujol's[17] records of three cases of myocarditis where mumps seemed the only exciting cause, there is little reference to the complication and none to a series of cases studied systematically for its occurrence. Rosenberg[18] recently observed two patients in whom there seemed no doubt that mumps was the exciting cause of heart block, and he was therefore prompted to make a careful study of the heart in a group of adults suffering from the disease. These two cases developed typical heart block confirmed by electrocardiogram (E.C.G.), one on the seventh and the other on the fifteenth day of illness. Both patients complained of retrosternal or precordial pain and experienced palpitations or dizziness. After a day or two the first patient developed a harsh systolic murmur at the apex which gradually diminished in intensity, and eight days after the onset of

[13] *Tubercle*, Lond., 1936, **18**, 292.
[14] *J. Amer. med. Ass.*, 1946, **130**, 1006.
[15] *Quart. Bull. Sea View Hosp.*, 1946, **8**, 5.
[16] *Quart. Bull. Sea View Hosp.*, 1936, **1**, 398.
[17] *Arch. de Med. et Pharm. mil.*, 1918, **69**, 527.
[18] *Arch. intern. Med.*, 1945, **76**, 257.

symptoms the E.C.G. was normal. The other patient, however, continued to show abnormal tracings until the seventy-seventh day of illness.

An electrocardiographic study of one hundred and four adults with mumps was then undertaken. Repeated examinations of forty-six of them were made at 2–4-day intervals. Abnormal records were obtained from 15%. There was no specific E.C.G. pattern, the most common abnormality being a change in the form of the P wave or a prolongation of the P–R interval. Fourteen of the patients showed more than one abnormality. Apart from one case all the changes occurred between the fifth and tenth days of illness, that is, at the same time as one expects to find other evidence of systemic dissemination of the virus. Subjective complaint was made by only four patients; in the others recognition depended entirely on the electrocardiographic examination.

The pathological nature of such changes must remain a matter of conjecture, but the findings raise the interesting question as to how far they are specifically caused by the virus. There is no doubt that myocardial damage may follow a severe virus infection such as influenza, and Finland and his colleagues[19] have reported two examples of non-bacterial myocarditis in which influenza (virus A) was the aetiological agent. It seems more likely, however, that the abnormalities reflect a non-specific myocardial lesion which might be a part of any acute infection. Indeed, Rosenberg avers that he has encountered similar changes not only in rheumatic fever but even in such mild infections as rubella. Watson, Rothbard, and Swift[20] recently recorded a study of one hundred and ten patients with scarlet fever who were investigated in a manner very similar to that of Rosenberg's study. In twenty-two instances they found abnormal E.C.G. patterns—most commonly inversions of the T waves and indications of transient partial heart block. In the majority of their patients the abnormalities were detected much later (tenth to fifty-sixth day of illness) than in the mumps cases, but like them many made no subjective complaint. Since they were dealing with a streptococcal infection it was natural to interpret their findings in the light of rheumatic fever and to consider that the fundamental tissue injury was the same in both. Rosenberg rightly argues, however, that delayed conduction time should not be regarded as a specific indication of rheumatic fever and that a recent acute febrile illness may induce E.C.G. changes which do not have the same serious significance.

The old clinical conception of myocarditis as a not uncommon complication of acute infections seems to gain some recognition from these findings. Is it possible that they may also explain the recrudescence of rheumatic fever sometimes seen in the course of an infection such as pneumonia in which haemolytic streptococci do not appear to have played a part?

19 *Amer. J. med. Sci.*, 1945, **209**, 455.
20 *J. Amer. med. Ass.*, 1945, **128**, 1145.
21 *Lancet*, 1934, **2**, 180, 236.

SYMPTOMLESS GLANDULAR FEVER

It was formerly said that glandular fever was seen more often in medical students and nurses than in any other classes of the community. This unusual incidence was attributed to the fact that the proximity of such patients to the laboratory attracted the attentions of the haematologist. Now the spread of institutional medicine and of clinical pathology has made it clear that glandular fever is not only a common disorder but one on which current views need to be recast.

Tidy[21] recognized glandular, febrile, and anginose types of the disease. Jaundice, meningo-encephalitis, parotitis, and a thrombocytopenic haemorrhagic state are noted by Bernstein[22] as acknowledged complications. But the epidemics described by Halcrow, Owen, and Rodger[23] in 1943, and by Van der Meer, Lutterloh, and Pilot[24] in 1945, have stressed a new aspect. The first started in an E.M.S. hospital, which was thereupon closed to further admissions. The blood of all patients in hospital and of some of the medical and nursing staff was examined; of these 296 persons 125 presented the clinical and haematological picture of glandular fever, and a further 165 had the characteristic blood and serological changes without symptoms or physical signs of the disease. The second group of authors made similar observations on an American Army unit of 600 men from which several cases of glandular fever had been admitted to hospital. Blood films from 522 healthy men were examined; in 217 "abnormal cells resembling typical mononucleosis cells" were seen. The agglutinins for sheep's erythrocytes were titrated in the sera of 74 of these men and figures above 1 : 56 found in 13.

Study of the epidemic in the E.M.S. hospital has provided conclusive proof that the haematological and serological changes regarded as characteristic of glandular fever can exist without any clinical signs of ill-health. The second paper is less well documented and in many cases the proportion of abnormal cells was below 5%. The familiar problem arises of whether the "glandular-fever cell" is specific in its diagnostic import. Such cells were found by these authors in percentages of 1–20 in blood films from 110 patients admitted to hospital with other complaints, and Downey and Stasney,[25] Warren,[26] and others have described their presence in a variety of unrelated conditions. Thus it seems unjustified to regard the finding of a few "glandular-fever cells" in the blood film as necessarily indicating glandular fever. The absence of heterophil agglutinins is of little significance unless the test is repeated frequently, for Himsworth[27] has reported an example in which the titre did not rise to a diagnostic level until eleven weeks after the onset. Even with these reservations Van der Meer, Lutterloh, and Pilot have confirmed the existence of this asymptomatic form of the disorder described by Reyersbach and Lenert[28] and the British observers.

Emil Pfeiffer's[29] concept of *Drüsenfieber* must now be expanded to include not only the variants which most clinicians have come to recognize but also this symptomless haematological disturbance. Moreover the experience of Halcrow, Owen, and Rodger suggests that the accepted view of its low infectivity must be revised, for of the sample of the population at risk which they examined 97.9% showed evidence of the infection.

22 *Medicine*, 1940, **19**, 85.
23 *British Medical Journal*, 1943, **2**, 443.
24 *Amer. J. med. Sci.*, 1945, **210**, 765.
25 *Folia haematol.*, 1936, **54**, 417.
26 *Amer. J. med. Sci.*, 1941, **201**, 483.
27 *Lancet*, 1940, **1**, 1082.
28 *Amer. J. Dis. Child.*, 1941, **61**, 237.
29 *Jhrb. Kinderheilk.*, 1889, **29**, 257.

ABSTRACT JOURNALS

Owing to printing difficulties it has, unfortunately, not been possible to publish *Abstracts of World Medicine* and *Abstracts of World Surgery, Obstetrics and Gynaecology* on Jan. 1 as advertised. Both journals should be published next week.

We regret to announce the death of Sir Richard Cruise, G.C.V.O., Surgeon-Oculist to King George V and Queen Mary and consulting surgeon to the Royal Westminster Ophthalmic Hospital.

THE FIRST ADMINISTRATION OF ETHER

Centenary Commemoration at University College Hospital

On Dec. 21, 1846, at University College Hospital, London, the first public operation under an anaesthetic to be performed in Europe was carried out by Robert Liston. The patient was a Harley Street butler, aged 36, who came for amputation of the right leg above the knee. At 2.25 on that day he was brought into the operating theatre; he breathed ether vapour for between two and three minutes, and the effect was such as to cause complete insensibility to pain, although consciousness was retained and questions were answered. Liston performed the complete operation in less than half a minute, during which not the slightest groan was heard from the patient nor was his countenance at all expressive of pain.

To commemorate this event a gathering took place at University College Hospital on Dec. 21, 1946, at which Dr. MASSEY DAWKINS gave a short address. The original operating table with the holes through which the straps were drawn to restrain patients in pre-anaesthetic days, a model of the original inhaler, and various contemporary sketches and portraits were exhibited, and a copy of the case notes of this successful amputation was handed to every visitor.

Dr. Dawkins said that an attempt had recently been made by Scotch friends to claim for a hospital in the North the honour of the first ether administration in the Old World, but the evidence was scanty (*Journal*, Oct. 26, p. 621), and the occasion was not in any sense a public one. Some idea might be obtained from Sir Rickman Godlee's biography of Lister of the state of pre-anaesthetic surgery at University College Hospital. The three senior surgeons operated only on Wednesday afternoons, and with such celerity that that time was sufficient for all the operations of the week, apart from emergencies. Patients requiring amputations were asked at the doors of the theatre whether they would have their leg off or not, and if they said "Yes" no heed was taken of any subsequent change of mind. Patients at first frequently refused to face the ordeal, then became resigned, only, many of them, to engage in a useless resistance at the last moment.

In October, 1846, the discovery of ether anaesthesia was announced in America. Liston witnessed its demonstration at the Royal Medico-Chirurgical Society, where Matthew Duncan was a volunteer. Liston was a surgeon of great skill and of forceful character, with remarkable dexterity in the use of cutting instruments. The operating theatre in which he worked was a semicircular apartment, about 40 ft. (12 m.) across, with sharply rising tiers of seats for the students. It contained a small basin, about the size of a soup plate, in which the surgeons washed their hands—sometimes even before the operation—and there were pegs from which hung the blood-stained frock-coats of the staff. Actually the first English operation performed under ether anaesthesia was a dental extraction carried out by Mr. Robinson, a dentist of Gower Street.

Liston's theatre had a noteworthy company, including Sir Russell Reynolds, Sir John Erichsen, and the future Lord Lister. Liston gave a short address describing the American discovery and the advantages to be hoped for, added a word about the weak condition of the patient, and appealed for quietness and consideration. The patient was brought in with a handkerchief covering his face. Ether induction took place quietly, and in twenty-six seconds the limb was off. The patient, rising as from ordinary sleep, then said, "Take me away. I cannot have it off. I must die as I am," and could hardly believe when it was proved to him that the limb was already amputated. He went on without interruption to a good recovery and was discharged from the hospital on the following Feb. 11. Sir John Forbes, one of the spectators, said that he never felt so near to falling on the floor in his life as he did when he witnessed the operation. Everybody was pale and silent, except Liston himself, who was flushed and excited, and could scarcely command himself to speak. When, after it was over, he broke the silence and said, "Gentlemen," he almost choked. According to Sir Russell Reynolds's account he said, before starting, "Gentlemen, we are going to try a Yankee dodge for making men insensible. This man's leg has to come off above the knee, and my friend Mr. Squire is going to give the ether so that the man will not feel it." The ether in those days was not as pure nor the apparatus as handy as now, so perhaps Liston was a little impatient to get on with his work. When Squire said he was ready, Liston's knife flashed in the air. "I took out my watch," said Reynolds, "and the leg was on the floor in twenty-six seconds." Liston turned to the company, "This Yankee dodge beats mesmerism hollow."

There was a curious incident of a student (or by some accounts a hospital porter) named Sheldrake, a man of powerful build, who volunteered to be anaesthetized in the theatre, but after half a minute's administration sprang from the table, felled the anaesthetist with a blow, swept aside the assistants, and tore up the gangway, scattering the students like sheep. The second patient on whom an operation was done under anaesthesia was an out-patient whose toenail was removed. On the same night, in a letter to a friend, Liston began with the words of St. Paul, "Rejoice, and again I say, rejoice." At dinner that evening he insisted on anaesthetizing his assistant. The assistant said afterwards that when he was about half under he heard one of the ladies say, "Mr. Liston, for God's sake, stop; you will be the death of this young man." He did stop, but the assistant felt the pressure of Liston's hands on the lobes of his ears for a day or two.

The lay press took no account of this historic happening until Christmas Day, when it was mentioned in the *Daily News*, sandwiched between paragraphs about the lateness of the Birmingham mail and a fracas of bedmakers and students at Cambridge. The *Times* did not notice it until Jan. 4, 1847. The change in surgery consequent upon the introduction of anaesthesia was a very gradual one. No striking new operations were introduced, no new fields opened up, operations were still performed at breathless speed, and students still saw the surgery of pre-anaesthetic days, robbed only of its most shocking feature, that of the pain inflicted. But the records of University College Hospital showed no cases of excision of the knee between 1830 and 1850, while in the next four years there were twenty-one cases. Ether was still the safest anaesthetic for general use, and despite the advances in other forms of anaesthesia the average yearly consumption of ether was now more than half a ton at each of the large London hospitals.

Dr. E. A. BARTON, whose father, then twenty-two years of age, was at University College Hospital and present on the occasion, added a few words. He recalled the smallness of the old theatre, how the students in their tiered seats looked down upon the patients. His father had told him that in the pre-anaesthetic days the one part of their training which the students could not stand was the surgery course, which was made dreadful by the shrieks and screams coming from the operating theatre and echoing through the hospital. The wooden table on which the operations were done had been rescued from a lumber room and was now a treasured museum piece at the hospital.

HEALTH ADMINISTRATION IN THE CITY OF LONDON

The development of health services in the City of London was the subject of interesting speeches at a luncheon of the Corporation health committee on Dec. 19, when a presentation was made to Sir George Elliston on the completion of his third term of office as chairman of the committee.

Sir ALLEN DALEY, President of the Society of Medical Officers of Health, pointed out that the Corporation had been issuing sanitary regulations as far back as 1281 and had continued to develop their health services from that time onwards. But the outstanding event in the health history of the city had been the appointment by the Corporation in 1848 of Sir John Simon as their first medical officer of health. For once London had to yield pride of place to Liverpool, who had appointed the first of all medical officers of health the previous year.

From Simon onwards the City could be relied upon to pick winners for its chief health officers. After seven years' service with the Corporation, Simon had become successively medical officer for the Central Board of Health and for the Privy Council, and the first medical officer of the Local Government Board. He had therefore been the first in line of the seven medical officers who had filled the City post now held with

such distinction by Dr. Charles White. He had also been the first in line of the chief medical officers of the Ministry of Health.

Hygienist and Surgeon

Simon had been not only a great nygienist but also a distinguished surgeon on the staff of St. Thomas's Hospital and sometime President of the Royal College of Surgeons. His reputation among scientists had secured his election as a Fellow of the Royal Society.

During his seven years in the City he had coped with an outbreak of cholera (1854). He had laid the foundation of the work of a public health department as we knew it to-day, but naturally with emphasis on bad environment. He had started house-to-house inspection and the registration of tenement houses; his had been the first annual report of a medical officer of health. His reports had been models of clarity and good sense. He had asked for power to control nuisances, unhealthy industries, the adulteration of food, and the sale of poisons. He had recommended that there should be one Minister of the Crown for all health purposes, but not till 1919 had we had a Minister of Health. On leaving the City he had expressed "grateful recollection of the years during which I have been a local officer of health." The citizens, he had said, had always treated him with favour and confidence notwithstanding all he had had to preach to them. In 1885 all the vestries in London had been required to follow the example of the City and appoint an M.O.H., and Simon had been very gratified that so many distinguished doctors had sought these posts.

The Corporation during the past 100 years had been responsible for much pioneer work in the City. Their chairman, Sir George Elliston, had claimed that they cared for the citizens from the cradle to the crematorium, and it was true that the City had set a high standard in the matter of infant welfare work just as they had been among the earliest municipal bodies to provide a crematorium. They had set an early example in securing open places for the recreation of the people; they had developed highly efficient port health services; through their markets and inspections they had done much to safeguard the food supplies of Greater London; finally, they had maintained through the centuries close connexion with the five royal hospitals.

Bart's and the City

Sir GEORGE AYLWEN, replying to the toast, said it was a matter for pride that St. Bartholomew's, founded in 1123, had for 8¼ centuries on the same site continued its benevolent work of tending and healing the sick. The history of the hospital was inextricably interwoven with the history of the City. It had been the citizens of London who, with their own hands, under the guidance of Rahere, had built the first St. Bartholomew's, and who had successfully petitioned Henry VIII to restore to them the ancient Foundation which he had suppressed. The legal title of the hospital was still "The Mayor and Commonalty and Citizens of London, Governors of the House of the Poor, commonly known as St. Bartholomew's Hospital." In early days the City Corporation and the hospital had not always been on good terms. In 1559 the governor had complained that the Lord Mayor was wrongfully withholding their water supply. In 1697 we found the hospital governors protesting vehemently to the City aldermen about a matter of £7,500—no mean sum in those days—which the aldermen had seemed disinclined to pay until the court of chancery had insisted that they should. In 1775 the Common Council had attempted to induce the tenants of the hospital to pay their rents to them instead of to the hospital governors. Since then times had changed, and he was proud to think that to-day, and for many years past, the hospital's relations with the City Corporation had been an object lesson to local authorities and voluntary hospitals alike.

Partners in Welfare

The hospital regarded it as a privilege to co-operate with the Corporation in providing those services which were essentially the responsibility of the medical officer of health. The Corporation in their turn regarded themselves as fortunate to enjoy the services which only a great hospital like St. Bartholomew's could adequately provide. There were no arguments, no troubles, no friction, no questions of prestige: just a sincere and mutual desire to secure for the patients the best possible treatment that medical and nursing skill could provide. He needed only to mention some of the services the hospital so willingly rendered the City. Since 1915 there had been established at Bart's the City's tuberculosis dispensary, and during these thirty years just over half a million attendances had been recorded. For nearly thirty years, first in Golden Lane and subsequently in the hospital, the governors had undertaken the provision of a special treatment centre for City patients suffering from venereal disease. From 1932 onwards the hospital's infant welfare clinic had been made the subject of an agreement with the Corporation whereby City mothers and babies could attend there at all times for attention and advice.

These and many other activities it had been the privilege of the hospital to undertake. That they had been successful there could be no doubt. But that success had been due not only to the part played by St. Bartholomew's: it had been due just as much to the help and co-operation received from the Corporation and its medical officers. Speaking as treasurer of Bart's, it might be hoped that under the National Health Service there would be left to them the opportunity and the privilege of continuing, with the Corporation as their partners, a service which had proved itself so outstandingly successful in the past.

REHABILITATION AND OCCUPATIONAL THERAPY CENTRE AT BROMLEY

A Rehabilitation and Occupational Therapy Centre at Bromley and District Hospital in Kent was opened on Dec. 14 by Sir Wilson Jameson, Chief Medical Officer of the Ministry of Health. Dr. Talbot Rogers stated in some introductory remarks that the hospital had received help from the Ministry in the form of equipment and of postgraduate facilities for those who would work at the centre. When fully started in the new year the department would employ eight physiotherapists. It was equipped to give all forms of electrical treatment except deep *x*-ray therapy. In the remedial gymnastic department emphasis would be laid on group methods in treatment. Patients would come to the department from the hospital or from other hospitals or be sent directly by local doctors. Dr. D. B. Whitlock and himself would supervise and co-ordinate the department, to which doctors would have full access and would be informed of the progress of their patients. Two ways in which the department expected to extend its activities were the provision of evening clinics and the use for mobile physiotherapy of a general purposes car which had been given to the hospital.

Sir Wilson Jameson, after an appreciation of Dr. Talbot Rogers's work on the Medical Advisory Committee of the Ministry and a word of praise for the Bromley Hospital as one of the best general practitioner hospitals in the country, went on to say that the sphere of usefulness of hospitals had tended to be limited to the more critical phases of ill-health, and too little regard had been paid to means of preventing physical breakdown or to the methods of rehabilitation. Great changes were likely to take place, however, and it was good to see Bromley well in the van.

"It should increasingly become the practice for patients requiring specially expert medical and nursing skill to seek such help in the well-equipped hospital of the future rather than in their own homes. The shortage of domestic labour and a growing appreciation of the importance of the ancillary medical services are already resulting in more numerous applications for treatment in hospital, and as soon as more adequate staff and accommodation are available hospital services will be more and more in demand."

The hospital of the future, Sir Wilson Jameson continued, would no longer be preoccupied with what might be termed the medical stage of ill-health, but would concern itself to an increasing degree with the primary and with the final stages—that is to say, with methods of prevention and of rehabilitation. In the past those patients who were debilitated by serious illness or unable to return to their former employment on account of severe disabilities left hospital in too many cases with little more than a recommendation that they were fit only for light work. Yet numbers of them, if only they had been taken in hand in time and provided with the necessary medical rehabilitation and vocational guidance, could have been saved from

chronic invalidism. It was in this respect that hospitals possessing modern rehabilitation departments could render such valuable additional service to the community. Physiotherapy and rehabilitation would form an essential part of the hospital and specialist services of the future. He added that a modern rehabilitation department should, wherever possible, be open in the evening as well as during the day. It should also be provided with its own almoner or social worker. It was important also that such a specialist service should never be divorced from the general practice of the neighbourhood. Hospitals which were already experimenting in this form of community service were meeting an astonishing response to their endeavours. One hospital which served a somewhat similar area to that of Bromley reported no fewer than 500 patients attending daily in its physiotherapy and rehabilitation department. In 1943 there were some 48 hospitals in England and Wales possessing all facilities for active rehabilitation; the latest figure he could give was 204, with a further 129 having partial facilities.

"The principle of general practitioner hospitals and departments is now widely accepted—always with the proviso that such a hospital or department should form part of a bigger scheme with suitable links with a larger parent hospital, preferably of teaching hospital standard."

Bromley provided an excellent demonstration of the importance of having hospital facilities readily available to the general practitioners of the area.

MEDICAL PHOTOGRAPHY

Increasing interest is being taken in the use of photography and cinematography for record and teaching purposes, and it has been found particularly valuable in the medical sciences. In accord with this the Institute of British Photographers has decided to allot one part (Section 4) of its final examination to medical photography. Candidates must have passed the Institute's intermediate examination, and therefore be acquainted with general photographic theory and practice, before sitting for the final, for which is required not only a higher standard of photographic knowledge but also a knowledge of such subjects as human anatomy and physiology, medical terms and their significance, the recognition of the regions and tissues of the body from photographs and skiagrams, and also the more general topics of medical etiquette, relations between photographer and doctor, nurse, and patient, the problems of working in operating theatres, and the risks of infection. Since much of the medical photographer's work consists of record photography, he must learn standardization of technique and record filing.

The qualified medical photographer must have a wide range of technique at his command. With the improved materials now available infra-red, ultra-violet, and fluorescence photography may be required, and he may also carry out miniature radiography, photomicrography, and stereoscopic photography.

The Scientific Film Association, 34, Soho Square, London, W.1, was founded in 1943 to provide information on and promote the use of scientific films. Membership is open to private persons, academic institutions, and commercial firms. It has issued several lists of films of medical interest, the latest being a *Catalogue of Films on Anaesthesia,* which includes notes on about twenty-five films.

A detailed account of each film is provided—running time, gauge, where made and by whom, etc.—but the most interesting feature is an "appraisal" that comments on the qualities of each film from every point of view—photographic, scientific, and educational. The Association has a viewing panel, which appoints appraisal groups of a "considerable size," to examine films selected by the appraisal committee. The constitution of these groups is kept as wide as possible so that every aspect of the film shall be judged, and they include medical specialists, house-men, nurses, students, photographers, and laymen. The result is admirable: appraisals seem to be entirely objective, and, indeed, sometimes severe. If a film is practically valueless in the opinion of the appraisal group the fact is recorded.

The whole range of anaesthesia is dealt with in this series—local, spinal, intravenous, and inhalation; and there are films on operative shock, the handling of the patient, and respiratory and cardiac arrest.

Reports of Societies

CARCINOMA OF THE STOMACH

A symposium on carcinoma of the stomach was held at two joint meetings of the Radiological Section of the Royal Society of Medicine and the British Institute of Radiology on Dec. 13 and 14. The chairmen at the sessions were Dr. S. WHATELY DAVIDSON, president of the Section of Radiology, and DR. H. W. SMITHERS, president of the Institute.

Radiology and Gastroscopy

DR. J. A. GROUT discussed the various sites and radiological signs of carcinoma. The radiologist should be able to distinguish between the ulcer and a cancerous lesion. The mucosa and the peristaltic waves, which only at the later stages stopped at the obstruction, needed careful examination.

Mr. H. W. RODGERS said that radiology and gastroscopy were complementary methods of examination. The principle that gastroscopy should follow *x*-ray examination was important. Gastroscopy was contraindicated in gross deformity of the oesophagus, spinal curvature, atrophy of lining mucosa, and if *x* rays demonstrated an advanced carcinoma. Gastroscopy was of value in clinically suspect cases which were obscure or negative radiologically, but the technique had definite shortcomings in not showing the whole area of the stomach. Of carcinomata, 10% were diagnosed by gastroscopy, but the whole position concerning gastric carcinoma was disquieting and every effort must be made to find precancerous lesions. Gastroscopy had made the diagnosis of early cases possible.

Pathology and Surgery

Prof. M. J. STEWART said he was impressed by the malignancy of the scirrhous cancer of the stomach, which recurred The fact of invasion of the lymphatic glands, not its extent, was the important point in ultimate prognosis. Concerning the spread of carcinoma of the stomach, it was remarkable how seldom it transgressed in the duodenum; when it did so it was always by submucous extension, and such cancers made their way back to the surface, giving the appearance of two independent cancers. He gave his own figures covering a twenty-year period, including over 700 cases. One interesting point brought out was the positions of chronic ulcer, ulcer-cancer, and primary cancer in 358 surgical specimens.

	Chronic ulcer %	Ulcer-cancer %	Primary cancer %
Pyloric end ..	5·7	29	84·5
Lesser curvature ..	94·3	71	10·7
Rest of stomach ..	0	0	4·8

For Mr. HERMON TAYLOR the outstanding clinical fact about cancer of the stomach was that, in itself, it was a symptomless disease; a large tumour might develop without being suspected by the patient. Bleeding of a sufficient degree to cause alarm was uncommon and pain was a later symptom. Unless the growth was in a position to cause obstruction there was no compelling reason which drove the patient to the doctor. The potential significance of the minor symptoms and correction of the misconception that cancer need only be postulated if symptoms failed to respond to treatment were important. Pyloric growths, as they might give rise to obstructive vomiting, were generally recognized earlier than the less common tumours of the body of the stomach. Ulcers which underwent malignant change were mostly situated near the pylorus, and the danger in these cases was that a new symptom might be regarded as part of the already established general picture. Persistent minor dyspeptic symptoms arising *de novo* in a patient over forty, or persistent vomiting in a patient with known ulcer, must be investigated for malignant disease before treatment was applied. Of thirty-eight consecutive patients, many of whom were diagnosed early by gastroscopy, no fewer than eleven showed histological evidence of their lesion having arisen in a chronic ulcer.

By modern radiological technique, supplemented where necessary by gastroscopy, the diagnosis of carcinoma of the

stomach could be established as a fact and not an opinion. An unequivocal filling defect shown by *x* rays needed no gastroscopic confirmation. But radiology and gastroscopy failed to estimate the operability of the lesion, demonstrating only its mucosal aspect, and giving no indication of lymphatic involvement. The question of operability could be decided finally only by the surgeon's hand within the abdomen. Adequate extirpation of the growth could be achieved in a large proportion of cases only by a wide dissection, as was illustrated by 17 cases of radical removal for gastric carcinoma in which one or two of the contiguous viscera were removed with the stomach. Of these 7 died as a result of the operation, but of the 10 survivors 8 were still alive after two or three years.

Radiotherapy

Dr. G. C. FAIRCHILD and Mr. ALAN SHORTER presented a joint paper on radiotherapy. They described the technique for direct irradiation of deep-seated tumours exposed temporarily at operation; intensities of 3,000 *r* in three minutes were used and radiation of the normal viscera so far as possible avoided. Of 15 cases of inoperable gastric cancer treated by direct radiation, the growth in 7 was so extensive that the radiation could be palliative only; among these the longest period of survival was six months. In 8 cases in which the growth was limited to an area which could be irradiated, the period of survival after treatment in one case was twenty-four months, in another fifteen months, and in the others shorter periods.

Dr. D. JENNINGS said that carcinoma of the stomach was the most important form of malignancy in Western civilization. The total yearly incidence of carcinoma of the stomach in persons under the age of 70 was 8,500. Of these cases 7,000 were referred to hospital; of these again between 3,000 and 5,000 were referred to surgeons; on these between 1,000 and 3,000 laparotomies were carried out; from 300 to 1,000 underwent a gastric operation; from 200 to 500 survived gastrectomy; and from 40 to 100 were 10-year survivors.

THROMBOSIS

A meeting of the Section of Pathology of the Royal Society of Medicine was held on Dec. 17, with Dr. A. B. ROSHER, president, in the chair. The members of the Surgical Section had been invited.

Pathological Post-operative Thrombosis

Mr. H. J. B. ATKINS, opening from the surgical side, said that thrombosis as a post-operative complication was increasing and there were many problems connected with it which the pathologist would be able to help the surgeon to solve. Thrombosis, of course, was a natural and physiological accompaniment of any operation. By post-operative thrombosis was not meant that natural occlusion in the veins at the site of operation which would normally occur, but a thrombosis which tended to spread or which appeared remotely. A question at issue was whether pathological post-operative thrombosis was due to a spread by continuity of natural thrombosis. He had analysed the records of a series of cases of post-operative thrombosis occurring at Guy's Hospital between 1921 and 1925, and during that time there were two cases of axillary vein thrombosis—one after a gastrectomy and the other after a prostatectomy—and two cases of left femoral vein thrombosis following radical mastectomy. An argument which was put forward to show that thrombosis in the leg veins was a spread from the site of operation was that thrombosis was extremely rare when the abdomen had not been opened. After laparotomy there was diminution of the respiratory excursion, and this would lead to a slowing of venous return, which was an important factor in the causation of thrombosis. Pelvic operations were peculiarly liable to be followed by post-operative thromboses, this suggesting that thrombosis extended from the operation site. But here age incidence should be taken into account: pelvic operations were performed more commonly on patients getting on in life, who were more liable in any event to thrombotic complications. Mr. Atkins felt that the continuity theory as an explanation of post-operative leg thrombosis should be discarded.

Why did the remote thrombus form? An operation occasioned various changes in the blood, an increase in the platelets and fibrinogen content—two factors closely connected with blood coagulation—and also a slowing of the blood stream consequent upon recumbency. Again there was the possibility of infection which might cause an endophlebitis predisposing to thrombotic complications. Why did thrombosis so commonly occur in the left leg? Venous circulation was sluggish after an operation, and more sluggish on the left side on account of pressure, perhaps by the sigmoid colon and iliac vessels. Anti-coagulation therapy protected the patient in a very large measure against the development of pulmonary complications. All that such therapy could do was to prevent the development of fresh thrombi; it could not influence the thrombus already present, and it looked as if it were only the freshly formed thrombi which were likely to cause pulmonary embolus. What clinicians would like to know from their pathological colleagues was how fresh the thrombus must be to cause pulmonary manifestations. Heparin and dicoumarol were agents which prevented thrombus formation, but the former had certain disadvantages and the latter some dangers. On the other hand, it was known that as soon as the patient got up the danger of the occurrence of thrombus was very slight. Could the duration of anti-coagulant therapy be shortened with safety?

Pathology of Primary Thrombosis

Dr. R. H. D. SHORT described an imaginary post-mortem examination of a case in which death had occurred from pulmonary embolism ten days after an operation. On opening the pulmonary artery a long coiled thrombus might be found, blocking both main branches. If the thrombus was taken out carefully and disentangled it would be found that over the greater part of its length it was unbranched, but there were branches at the upper and lower ends, one end being paler than the other. If sections were made of the pale part the typical laminated structure characteristic of ante-mortem clot would be found. The upper end of the thrombus would appear rounded, and the other, the pale end, obviously broken. From the length of the clot it might be assumed that it came from either of the two femoral veins. If those veins were now opened one of them might be found to contain a long eel-like thrombus and the other to be empty. Somewhere near the level of the knee would be found a broken end which corresponded with the broken end of the thrombus in the pulmonary artery. If further examination were made of the veins of the lower limb it would be found that the primary thrombus in a large proportion of cases arose in the muscular branches of the posterior tibial vein. When once organization had occurred the tendency to embolism would be enormously reduced, and there was evidence that organization occurred very rapidly, though it might not involve all portions of the thrombus at the same time. Thus a certain interval might elapse before the whole of the thrombus was organized on to the vein wall. Lesions in the media of affected veins were the result rather than the cause of thrombosis. He discussed the factors favouring embolism and said that the essential problem of thrombosis was why the platelets deposited where they did.

Dr. HELEN PAYLING WRIGHT spoke of the modern experimental approach to the study of platelets. The precipitating cause of thrombosis was far from clear, but after operation there was an increase both in platelets and fibrinogen, reaching their maxima about the tenth day coincident with a slowing of the blood-flow. Young platelets were more adhesive than older ones—a characteristic common to all young blood elements. She discussed the adhesiveness of platelets and gave an account of some experiments which suggested that adhesiveness was due to a surface film of fibrin.

Mode of Action of Anti-coagulants

Prof. H. P. GILDING said this stickiness of the cells must somehow enable them to release the kinase and so initiate thrombosis. Dicoumarol as an anti-coagulant would inhibit the formation of prothrombin in the liver, but such inhibition took time. A more rapid inhibition might be brought about by the injection of an adequate amount of heparin. With this substance it would take place within a period of seconds, depending on the circulation time from the vein into

which it was injected. Heparin affected the stickiness of the platelets and tended to prevent them from agglutinating and perhaps from disintegrating. Should one use vitamin K or a transfusion after excess anti-coagulation therapy? For a quick reaction a transfusion of normal blood in adequate amount should be given, at the same time giving the patient vitamin K so that he could rapidly manufacture his own.

Mr. D. H. PATEY said that if a fatal thrombosis occurred it was commonly supposed that it was likely to happen on the tenth day after operation. But it might occur on the first or second day; a surgical colleague of his had a fatal embolus in a patient on the way back from the theatre. It was a question whether the static factor at operation might not have an effect, and it had been suggested that any increased incidence of thrombosis might be referable to the longer time taken over operations. One impediment in the way of research and further knowledge was the fact that these occurrences were relatively so infrequent. Hospitals were appointing resuscitation officers, and they might usefully be employed also as thrombosis or pulmonary embolus officers.

Mr. SOLLY COHEN said he had had a patient die on the table from pulmonary embolus. It seemed particularly important that, before operation on a patient who had had a long rest in bed such as for gastric ulcer, the subject should be ambulant for at least a week. Dr. SHORT, replying to a question, said that a thrombus under 15 cm. in length was not likely to cause sudden death; the thrombi which did produce sudden death were of 45–50 cm. length. So far as the effect of pressure was concerned it was a peculiar fact that it was not the more superficial of the calf muscles which were involved but the deeper soleus muscles.

CARE OF CHRONIC SICK: CONTRIBUTION OF PHYSICAL MEDICINE

At the meeting of the Section of Physical Medicine of the Royal Society of Medicine held on Dec. 11 Dr. F. COOKSEY presided, and referred with great regret to the death of Dr. A. R. Neligan, who was to have been one of the openers of the discussion, and whose paper would be read by Dr. F. I. DAWSON.

Dr. E. L. STURDEE said that the problem of the chronic sick was becoming greater because of the larger number of old persons in the population. In Great Britain in 1901 there were only 1,750,000 persons over the age of 65; in 1941 this number had increased to 4,300,000, and by 1951 it was estimated that it would have reached 5,000,000. An investigation in Surrey, however, had disclosed that 29.6% of the chronic sick in that county were under the age of 65. Owing to housing and economic conditions many of these people who would have been nursed at home were seeking admission to hospitals and occupying badly needed beds. Public opinion—and medical opinion in particular—must be educated to the fact that the chronic sick constituted a problem with which it was not beyond medical knowledge to deal. If every hospital took long-term patients medical students would realize the problem which would continually face them in private practice, and some at least would be interested enough to specialize. All chronic patients could not be cured, but they could be accommodated in annexes, perhaps in the hospital grounds or at all events near the hospital, and under its supervision. Here they would be able to get about, though still needing medical oversight, and could live in conditions more nearly resembling those of a private home. Such annexes would not require nursing and domestic staff in the same proportion as the hospital proper. The general public, and especially the medical and nursing professions, must be made to realize that patients suffering from chronic illness had as much right to treatment as those with acute ailments.

The paper by the late Dr. A. R. NELIGAN detailed certain general and special methods of treatment.

Dr. MARJORY WARREN discussed clinical aspects of the chronic sick. She emphasized the need for treating the patient as a whole—physically, psychologically, and socially. An atmosphere of optimism in rehabilitation was necessary. Patients might become bedridden in various ways, and some were confined to bed because of inadequate help for some minor lesion; for example, an old man whose only trouble was stiffness in the hands, and who was unable to dress himself. Some old people were put to bed by indulgent relatives. Other chronic cases had been mismanaged and were suffering from loss of morale. There were those who preferred to remain bedridden as the only way of avoiding a return to unsatisfactory social conditions.

Treatment must be energetic and optimistic, and the patient must be inspired with confidence in his doctor. It was important to keep patients moving in bed, and as soon as possible to get them up, even if only for a short time. They should be encouraged to sit up to all meals and dress when able. It should be explained that this was not for the convenience of the staff but because it gave better limb movements than any other form of exercise. A hemiplegic should be given a full range of shoulder movements two or three times a day by the nursing staff, and if possible should be encouraged to do them on his own. Occupational or diversional activities should be arranged as soon as possible. Patients in the active stage of treatment should be separated from those in the earlier stages or the completely bedridden. From the psychological point of view it was most important that the doctor should discuss the patient's condition with him. It was necessary to keep in touch with relatives and friends. When treatment was prescribed the doctor should see that it was carried out fully, and he must obtain the co-operation of the nursing staff. Adequate nursing staff was a first necessity, and when it was not possible to get enough trained nurses, nursing attendants were useful.

CHILDBEARING: SOCIAL AND ECONOMIC PROBLEMS

An inquiry into the maternity services of this country, and especially into the social and economic problems of the young mother, is being made under the auspices of a joint committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee. Two years ago a grant of £5,000 per annum for five years was made to the Population Investigation Committee for the purpose of research, and it was decided that an inquiry into maternity services would be most appropriate. Dr J. W. B. DOUGLAS was appointed research officer, and at a meeting of the Eugenics Society on Dec. 17 he gave an interim report.

The inquiry has been aimed at discovering what use the mother made of the maternity services; the cost, including medical costs, of her confinement; the regional differences between the services provided for mothers; the incidence of breast-feeding; and a number of other facts. It was considered that the information could be obtained only by a direct approach to mothers all over the country; the interview was preferred to the questionary, and it was necessary that the interviewers should have a knowledge of maternity and child welfare. Health visitors were the obvious people to undertake this task. The co-operation of the Society of Medical Officers of Health and of individual local authorities was secured for a scheme whereby health visitors were requested to interview all mothers delivered during a single week in March last. Out of 458 local authorities in Great Britain, 424 agreed to participate in the survey; the remainder were unable to do so owing to shortage of staff. The field workers thus engaged were given a list of questions which had a very wide range, from such matters as antenatal care and the use of analgesia at the confinement down to the number of napkins in use for the baby and the cost of the perambulator. The mothers were interviewed two weeks after delivery. About 150,000 forms were completed; 2% of the mothers refused to co-operate, and 8% could not be traced.

The full report would not be ready until June, 1947, but some preliminary results were available. Grouping the women according to the employment of their husbands, a professional group accounted for 8%, black-coated workers 10%, and manual workers 65%. In the professional group one birth in every twenty was that of a fourth or higher number child, in the black-coated group one in every ten, and in the manual group one in every four. In the professional group those who were living in a population density of two or more for every bedroom and living-room—a high degree of overcrowding—numbered one in twenty, in the black-coated group one in ten, and in the manual group one in four. Considering the high proportion of wives of manual workers who had their babies at home this last was a shocking figure.

Antenatal visits were almost universal; only 65 mothers had no care at all, and these were mostly mothers of illegitimate children who had concealed their pregnancies. On the average the professional group started to have antenatal care in the third month, and the wage-earners and manual workers in the fourth. The whole position with regard to antenatal care seemed to be most satisfactory. Most of the professional class went to their private doctors, and most of the manual workers were taken care of by the local authority.

Care during the Confinement

It was in the care of delivery that the greatest differences showed themselves between the groups. The wives of men in the professional class received all round a higher standard of attention than did the wives of manual workers, and the wives of black-coated wage-earners came somewhere between. One out of every ten mothers in the professional group was delivered by a specialist; the corresponding figure for the wives of manual workers was one in fifty. Home delivery was much more common in the manual worker group. One in five of the women in the professional group was delivered at home; the figures for the other two groups were one in three and one in two, respectively. One in three of the professional group was delivered in a nursing home, but only one in seventeen of the wives of manual workers.

It might have been thought that in the same type of institution the members of the three social classes would receive the same quality of treatment, but this was not so. At home the mothers in the professional group were mostly attended by their own doctors; the wives of manual workers by midwives. Three out of five in the professional group who were delivered at home received analgesia, but only one out of five in the manual worker group. The same sort of difference obtained in institutions and hospitals. The proportion in the professional group who, being delivered in hospital, received analgesia was much greater than in the manual group, the black-coated wage-earner group again occupying an intermediate position.

The same social distinction obtained in respect to the length of time spent in hospital. In the professional group the mothers stayed in the nursing home or hospital for an average of thirteen and a half days, the wives of black-coated workers for thirteen days, and those of manual workers for twelve and a half days. Behind these averages were hidden, for example, the fact that those in the professional group rarely left hospital before the tenth day, whereas the wives of manual workers might have to leave hospital five days after the birth. These differences were not reflected in the averages.

The incidence of postnatal examinations, the question being put eight weeks after delivery, was rather low in all the classes. Only four out of ten in the professional class and three out of ten in the manual worker class had had an examination by a doctor since the birth.

The figures were very consistent in showing how far the country was from achieving any equality of care of mothers as between different social groups. Such equality could not be obtained without a very considerable extension of existing services and the education of expectant and nursing mothers.

CHEMICAL MECHANISMS OF DEFENCE

Some of the chemical methods employed by the human body to rid itself of poisonous substances were described by Dr. C. R. HARINGTON, F.R.S., of the National Institute for Medical Research, when he delivered a Friday evening discourse at the Royal Institution on Dec. 13, taking as his subject "The Body's Chemical Mechanisms of Defence."

Dealing first with substances of relatively simple composition, he pointed out that, apart from excretion, oxidation was the simplest process used. Certain amines which, although toxic, might be produced in the intestine were easily oxidized (mostly in the liver) to the corresponding and relatively non-toxic acids. These might either be excreted as such, or converted by conjugation with another compound into the excretory product.

One of the commonest and earliest recognized of conjugation reactions was the formation of the so-called ethereal sulphates—sulphuric acid esters, production of which in small amounts from food containing aromatic hydrocarbon groups was a normal physiological process. Benzene and other aromatic hydrocarbons, if absorbed from outside, were dealt with in the same two stages—oxidation followed by conjugation to form an ester.

Aromatic hydroxy compounds, he proceeded, as well as many hydroxy compounds in the aliphatic series, might also undergo conjugation to form glucuronides, which like the ethereal sulphates were readily excreted in the urine. The same process was also applicable to aromatic acids and acetylsalicylic acid, while in some animal species the conversion of certain terpene alcohols, such as borneol, into the corresponding glucuronide was so extensive as to form a reasonably convenient basis for the preparation of glucuronic acid.

As an example of the combination of aromatic and other carboxylic acids with nitrogenous compounds, Dr. Harington instanced the conjugation of benzoic acid with glycine to give hippuric acid. This reaction was common to many species and applied to many derivatives of benzoic acid, in addition to providing the second stage in the detoxication of substances such as toluene which contained oxidizable side-chains.

Species Differences

The detoxication of carboxylic acids showed species differences. Benzoic acid was conjugated with glycine in mammals, but with ornithine in birds to form ornithuric acid; and phenylacetic acid with glutamine in man and the chimpanzee, with ornithine in birds, and with glycine in the dog, cat, rabbit, and monkey.

With organic bases detoxication was by alterations in the basic group, the commonest change being acetylation. This was the general reaction with aromatic amines, such as aniline and its derivatives, including the sulphonamide drugs. Excretion was not, however, necessarily facilitated, and the products of certain sulphonamides might be an embarrassment.

Chemically, one of the most interesting conjugations was that with acetylcysteine to form the so-called mercapturic acids. This took place most characteristically with the monohalogenated benzenes, and involved the direct linkage of the nuclear carbon atom of the benzene ring with the sulphur of the acetylcysteine. Because of this conjugation, prolonged administration of bromobenzene might lead to cystine deficiency with delay of growth in young animals.

Antibodies and Allergy

The second and major part of the discourse was devoted to the antibody mechanism on which Dr. Harington has himself made important contributions. In contrast with the variety of defence processes invoked by relatively simple compounds there was here a single mechanism of extreme specificity. This was true of the response, not only to natural proteins, but also to proteins which had been artificially altered, specificity in the latter case being determined by the new groups which had been introduced. Thus iodinated horse serum raised antibodies in the rabbit which were inactive against untreated horse serum protein, but would react by precipitation with other proteins, including egg albumen, which had been iodinated. Similarly, if sugar-protein complexes were prepared by the azo-coupling method, familiar in dyestuff syntheses, the antibodies raised were determined by the nature of the sugar, even small stereochemical differences being detectable. Finally, Dr. Harington had himself been able to show that an antiserum prepared against a protein which had been combined with thyroxine could neutralize thyroid protein in which thyroxine was naturally combined. This was a physiological demonstration of the defence method against such a toxin.

Anaphylaxis and allergy appeared as an embarrassing variant of the same mechanism. A wartime example of sensitization was contact dermatitis from tetryl (2, 4, 6-trinitromethylnitraminobenzene), an explosive which had to be made in large quantities. The experimental sensitization of guinea-pigs, first with tetryl and then with related substances, had made it clear that the action depended on the formation, after absorption through the skin, of trinitrophenyl proteins which acted as antigens. The resulting antibodies, which caused the skin lesions, reacted to trinitroaniline compounds and to compounds which could form this group by combination with protein.

Correspondence

The Decision

SIR,—What proportion of the profession can the individual doctor count on refusing to enter the new Health Service? The result of the plebiscite gives some sort of guide, but a much firmer guide is essential before the average doctor would risk refusing, whatever his opinions of the Health Service Act and however strong these may be.

Surely the only solution is for the doctors in every district to get together in small groups at the earliest possible date to discover what each individual is likely to do. He should not be asked, "Do you intend to enter the Service or not?" but the qualified question, "If you were assured that a large majority of the profession is going to refuse to enter the Service, would you?" The results of these meetings should be sent to B.M.A. Headquarters through the Divisions, and B.M.A. Headquarters should keep the groups informed at frequent intervals through the Divisions what returns are coming in from other districts.

It is only if we who individually object to the new Act know what the rest of the profession is going to do that we could contemplate refusing to enter the new Service on the appointed day. Discussions on the Act and alternative proposals for an amended Act are out of place at this stage.—I am, etc.,

Sevenoaks. D. E. YARROW.

The Need is Unity

SIR,—The *Journal* of Dec. 21 makes inspiring reading. The profession, whose attitude has been so strikingly demonstrated by the result of the plebiscite, may feel pride in its leadership. Its determination to resist bureaucracy and dictatorship has been clearly expressed. The battle is joined and we shall need to muster all our determination to carry it through.

The immediate economic prospect facing practitioners who follow the Council's lead and refuse service under the Act is a stern one. On the "appointed day" they will, of course, lose their insured patients, while the unfortunately not inconsiderable disloyal minority will be in a position to secure large practices very quickly. Specialist appointments will also be affected by this position. This economic struggle will call for the greatest fortitude, but it is better for the majority of the profession to see it clearly in good time. Under the leadership of Dr. Dain and the Council they will surely feel that the struggle is worth while if it leads to the overthrow of the Act. In the words of your leading article, the paramount need of the profession at this moment is indeed unity.—I am, etc.,

London, W.9. A. L. JACOBS.

The Plebiscite

SIR,—Two of your correspondents reject my contention that the Labour Government has a clear mandate from the electorate to pass the Health Act on the grounds that the details of the Act were not published at the time of the election. Dr. A. K. Young (Dec. 21, p. 960) goes further and writes that "the great majority of the electorate are totally incapable of giving any intelligent mandate to anybody on their own account." That's as may be. Political parties lay down the general lines of their policies and rightly claim a latitude in their execution. They could hardly do otherwise without infringing the right of Parliament to shape its own Acts. In the case of the Health Act the Labour Party had indicated its intentions in great detail in a pamphlet called *National Service for Health*, which was published in 1943. The Act in no way conflicts with this announced statement of policy. No number of red herrings can alter this fact. In addition it should be noted that parties voting for the Act represent 15 million voters, while those who voted against represent only 10 million. This is conclusive.

Dr. H. M. Stanley Turner (p. 961) claims that the Act is a purely political matter. Of course it is. The Labour Party is giving practical expression to its own political philosophy, of which he happens to disapprove. I cannot agree with him that the 1944 plebiscite was "a confusing document." Many categorical questions were asked and answers given—e.g., a majority approved "negative direction." A study of the results will prove my contention that the B.M.A. Council and the Negotiating Committee are out of line with the profession as a whole.

I accuse many opponents of the Act of being concerned primarily with their own interests and liberties and very little with those of the community. I accuse them of remaining silent during the years before the war when unemployment and starvation conditions were creating ill-health, and of rushing to print when their own standard of life is allegedly affected. I accuse the B.M.A. Council of adopting a narrow sectional viewpoint at a time of immense social change when it should be leading the profession towards the creation of a great health service—I am, etc.,

Bristol. H. B. O. CARDEW.

The Plebiscite and the S.R.M.

SIR,—The Council is to move the following motion at a specially summoned Representative Meeting on Jan. 28:

"That the Negotiating Committee be advised that in view of the results of the plebiscite the Minister be informed that, because of the divergence between the principles of the profession and the provisions of the National Health Service Act, the Committee is unable to enter into discussions with the Minister on the Regulations to be made under the Act."

It has frequently been suggested that the decisions reached at Representative Meetings do not represent the views of the profession, and that persuasive oratory on the platform has played too important a part in its deliberations. At this crucial moment we should convince ourselves and the outside world that neither of these suggestions is correct by ensuring that our Divisional meetings are fully attended, and that our representatives are adequately briefed.

There is one further point which I should like to put forward for consideration. At the Divisional meetings which are to be specially summoned to discuss the Council's motion, each doctor should be handed a piece of paper upon which he will be asked at the end of the discussion to answer a plain "Yes" or "No" in favour of or against Council's motion. These slips should be handed to each doctor so that there will be no necessity for signatures, and the secrecy of the individual doctor's vote will be obtained. The final voting figures should be announced by the Divisional chairman at the end of the meeting. If every Division in the country sent its representative to the Special Representative Meeting armed with these figures (and the total votes for and against should be publicly announced from the platform), I feel sure that they would reveal the fact that the profession is at last fully aware of the implications of the "Willesden affair" and what it may expect in the future.

I have written this letter with the approval of the chairman of my Division.—I am, etc.,

R. PROSPER LISTON,
Representative, Tunbridge Wells Division.

Goodwill of Practices

SIR,—I would draw attention to the eloquent letter of protest, as published in the Press, sent to the Government by the representative bodies of the Insurance Companies and Investment Trusts, in which they condemn the proposed unilateral method of affixing the purchase price of compulsorily acquired property. This is just what the Government is going to do to myself and the thousands of G.P.s who own their own practices. My practice represents my life's savings, and yet under the new Health Act I shall be compelled to sell out to the Government at their price, which may or may not be a fair valuation.—I am, etc.,

Whitchaven. T. S. L. JONES.

National Health Service Act

SIR,—Now the fight is on I think to begin with the B.M.A. should make an effort to give the public the true facts about this Health Act. The facts, which I think are correct, are as follows. The late Government planned the Bill in the form of a White Paper which was handed to the profession for their

consideration and advice. Little alteration in this White Paper was considered necessary, and that little was agreed to by the Government, but unfortunately before it could be made into a Bill the Government was out. As soon as Mr. Aneurin Bevan was made Minister of Health our representatives approached him regarding the Bill, but were told he was too busy with housing to talk about health, despite the fact that the present Act was being prepared at that time. When we got to know this our representatives again approached the Minister with a view to negotiation and discussion, but the Minister then said he was negotiating or discussing the Bill with no one.

Surely we, the persons who are mainly responsible for running the Service, should be the ones to know how it should be organized to the best advantage of the public. Mr. Bevan has stated that the Bill has been passed and is the wish of the people of this country, but I maintain that it is an Act made by Mr. Bevan to nationalize medicine with no consideration for either the sick patient or the doctor.

I think it is time Mr. Aneurin Bevan realized that when he was appointed Minister of Health he became a servant of the Crown and thereby of the people of this country, and cannot use dictator methods such as were used in Germany and Italy and which were the cause of the last war.—I am, etc.,

Sutton in Ashfield. JOHN ANDERSON.

SIR,—The matter appears to me to be supremely simple. I am not interested in the details of furnishing, decoration, or equipment of a house which I believe to be structurally faulty and dangerous, and which will apparently be the only house in which I shall be allowed to live. I have no desire to emulate the immortal Florrie Forde and be admired as a very useful bird in a finely gilded cage. Unless the builder is prepared to remedy its structural defects I am not interested in or tempted by details of its beauty or comfort.—I am, etc.,

Rotherham. G. H. SEDGWICK.

SIR,—In the next week or two B.M.A. Divisions will be called upon to discuss and instruct representatives whether or not to support the Council's resolution that the Negotiating Committee should not enter into discussion with the Minister concerning the regulations to be made under the Health Act. It is important for each one of us to realize what exactly this implies and to consider whether or not it circumvents the already declared view of the majority of the profession as expressed in the B.M.A. referendum of 1944.

The issue, as recently restated by the Chairman of Council at Exeter, is, Does the Act sufficiently conform with the principles of the profession to permit further negotiation with the Minister? What are these principles? Close examination shows them to be no more than a thinly disguised stratagem to have excluded from the Act the prohibition of the buying and selling of practices, payment partly by basic salary, partly by capitation fee, and what is misrepresented as direction of the doctors. There is not the slightest doubt that the enabling Bill demanded by Dr. Dain in the same speech would have for its purpose the exclusion of these particular clauses. With regard to these three issues the 1944 plebiscite showed the Council of the Association to be quite out of touch with the opinion of the profession as a whole, and this was particularly evident in the case of the younger doctors represented by the Forces. It is greatly significant that the present plebiscite reveals this tendency still to exist, as doctors with 14 years' experience and under show a majority in favour of negotiation.

It would be difficult to deny that the Council has consistently ignored the results of the 1944 questionary, and, far from democratically accepting the majority point of view on these important issues, has, by a persistent and often emotional propaganda campaign, endeavoured to impose its own view on the profession. To that end, in the present plebiscite, with the voting forms were issued a statement condemning the Act and a letter from the Secretary which was not likely to impress the doctor in its favour. There was at the same time published in the *Journal* the speech by Chairman of Council at Exeter, in which he practically advised the doctors to say "No."

In spite of all these manœuvres a majority of less than 8% of the profession actually voted "No." This can hardly be regarded as the "substantial majority" laid down by the last Representative Meeting. In the forthcoming Divisional meetings the issue which has really to be decided is whether or not the present Council or the profession as a whole is finally to determine policy. It is not without significance in this respect that the proposer in Council of the resolution presently before the doctors is that same member of Council who, in 1944, before the Act was even conceived, resisted the election of the present Negotiating Committee for the purpose of consulting with the Minister concerning the future health services of the country.—I am, etc.,

Edinburgh. S. LIPETZ.

The B.M.A. and Public Relations

SIR,—As the issue has now been joined with the Ministry of Health over the new Health Service I wish to suggest that every attention be given to the publicity side of the campaign. It is always said that however popular individual doctors may be, the medical profession as a whole has had a bad Press. It is absolutely vital that the public should appreciate the various points in the new Act which we consider are so unsatisfactory to them and to us. Public meetings should be called in the big towns to ventilate the questions and inform public opinion. It would be a great help if medical men were furnished with a concise tabulated statement giving them the salient points in the matter and the vital principles involved, to convince the waverers and to provide the whole profession with the necessary ammunition. The many channels of advertising should all be employed. There can be no better use of the fighting fund than to devote a portion of it to securing more public support, without which there is little prospect of real success.—I am, etc.,

St. Leonards-on-Sea. W. GOVER.

The Unstable Adolescent Girl

SIR,—The appendix to the Report of the Committee on Psychiatry and the Law published in the *Journal* of Dec. 14 (p. 909) and the leading article in the same issue (p. 904) draw attention to an urgent social problem. While agreeing with the writer of the leader that "doctors and magistrates alike have approached their problem in a realistic and scientific spirit," it seems unfortunate that the appendix as published should contain a number of misleading statements. Take, for example, the sentence, "In many ways girls of higher intelligence are more dangerous to the community than girls of a lower intellectual capacity" (paragraph 34); or, "if it [the I.Q.] is above 70 they are apt not to be regarded as mental deficiency cases because of a misinterpretation of the Mental Deficiency Acts" (paragraph 10). No statement is forthcoming, however, to explain which cases may be dealt with under these Acts.

In the first paragraph the committee describe a particular type of girl with whom they are concerned, yet in the ensuing paragraphs deal with mentally defective, morally defective, socially defective, psychopathic, and—in that some are expected to respond to psychiatric treatment—psychoneurotic cases, as though they presented a single problem.

Clinical observation and detailed study of the unstable adolescent girl have shown the importance of basing diagnosis upon both mental capacity and social maturity, and of giving due consideration to the home circumstances before arriving at a recommendation. If a girl's intelligence quotient is below 70 the degree of incomplete development of mind is such as to warrant her being regarded as simple-minded. Whether she will require to be dealt with under the Mental Deficiency Acts will depend upon the extent to which she is also socially defective and the ability or otherwise of her parents or guardians to exercise the necessary care or control for her protection. If a girl's intelligence quotient is between 70 and 90 she should be regarded as being intellectually dull. In an exceptionally good home environment she may respond to supervision while on probation. If she shows strongly vicious or criminal propensities she can be dealt with under the Mental Deficiency Acts as being a "moral defective," but cannot strictly be dealt with as being "a feeble-minded person" if the intelligence quotient is more than two or three degrees above 70. The majority of girls in the dull group will require a period of from two to three years in a residential school or training

centre. Some will respond satisfactorily to this lengthy period of discipline and character building; for others the provision will prove to have been purely preventive. In relatively few of the cases in which the intelligence quotient is below 90 will there be any permanent response to psychiatric treatment. In those cases in which the intelligence quotient is 90 or more (and I.Q.s as high as 140 will be encountered among those who are persistently delinquent) the primary need is to determine the level of social maturity. In the absence as yet of a social maturity scale of general applicability the most reliable guide is a study of the girl's personal history from infancy onwards. Precocious physical and emotional development is a common feature in the history of the more intelligent girl, and absence of understanding, help, and advice on the part of parents or teachers a contributory factor. It is this group of cases that provides the most favourable material for psychiatric investigation and treatment.

When the committee have obviously gone to much trouble to collect and sift facts relating to the problem of the unstable adolescent girl it seems unfortunate that the above general principles upon which recommendations must be based have not been more clearly enunciated.—I am, etc.,

Liverpool. MURIEL BARTON HALL.

Migraine and the Sympathetic Nervous Pathways

SIR,—Mr. G. F. Rowbotham's article (Sept. 7, p. 319) on "Migraine and the Sympathetic Nervous Pathways" has just come to my notice. Several points seem worthy of comment. It is noted that Case IV did not respond satisfactorily to surgery. This it is felt could have been avoided by not subjecting him to the operation. The procedure we have adopted should obviate surgery on cases unlikely to respond.

I have personal experience of three cases of migraine which we have cured by cervical sympathectomy. In the first case stellate ganglionectomy was performed on account of status anginosus, and it was noticed that a left-sided migraine which had been present for years was abolished. The second case was that of a woman of rather neurotic tendencies who complained of a unilateral migrainous type of headache. In view of the possibility of a psychogenic origin it was decided to determine before embarking on any surgical procedure whether it was likely to improve her condition. Mr. Trumble first of all injected the region of her cervical sympathetic with normal saline, with no effect on her headache. He then substituted "novocain," and with the appearance of a Horner's syndrome the headache was abolished. The cervical sympathetic chain was then divided under local anaesthesia, and on stimulating the cut end of the latter the patient complained of having her "headache." Following operation she has remained well and has had no sign of any recurrence of symptoms over a period of nearly two years.

In the third case the patient complained of typical unilateral migraine of many years' duration. During an attack I injected her cervical sympathetic with "novocain," and with the appearance of a Horner's syndrome the migraine was abolished. Mr. Grayton-Brown performed a cervical sympathectomy, but could not reproduce her migraine by stimulating the cut end of the sympathetic chain. She has so far remained well and free from any untoward symptoms.

Three other cases in which operation might easily have been undertaken were found not only to be unrelieved by local anaesthesia of the cervical sympathetic but were made worse by it. Thus three failures were avoided. I would like to suggest to Mr. Rowbotham that he adopt the simple procedure of infiltrating the cervical sympathetic with "novocain" prior to operation so that cases suitable for this form of treatment can be selected. The ligation of the external carotid does not seem to be necessary and was not carried out in any of our cases.—I am, etc.,

Melbourne. S. A. SEWELL.

Mental Deficiency

SIR,—I wish to draw your attention to what appears to be an inaccuracy in "Any Questions" under the heading "Mental Deficiency" (Dec. 14, p. 929) where there appears the statement, "The sole criterion is what is best in the interests of the child." Although that may have been the standard until recently, the Education Act of 1944 gives to local education authorities the power to order special educational treatment for mentally deficient children not only in their own interests but also in the interests of the other children in the school which they would normally attend. The relevant section is 57 (4), which states:

> For the purposes of this section, a child shall be deemed to be suffering from a disability of mind of such a nature and extent as to make him incapable of receiving education at school not only if the nature and extent of his disability are such as to make him incapable of receiving education, but also if they are such as to make it inexpedient that he should be educated in association with other children either in his own interests or in theirs.

I think you will agree that although the ten-year-old mongolian idiot may be quite happy in the village school, the local education authority would be justified in removing the child in the interests of the other pupils.—I am, etc.,

Leeds. MARY N. M. PAULIN.

Use of Penicillin Pastilles

SIR,—Dr. G. C. Pether's letter (Dec. 14, p. 920) on the possible dangers of oral penicillin may indicate a rather wide interest in this matter and one or two further points may be made. The correspondence, to which a number of the readers of this *Journal* have contributed, arose from a Question and Answer in the issue of Sept. 21 (p. 447). Your technical expert there stated that stomatitis after oral penicillin was rare, only four cases having been reported. In subsequent issues there have been a number of letters reporting further cases, and the impression is growing that commercial penicillin pastilles supplied for the local treatment of sensitive oral infections may be quite a frequent cause of sore tongue and sore mouth. The matter seemed to be clinched by the communication of Drs. Ellinger and Shattock, "Nicotinamide Deficiency after Oral Administration of Penicillin," in the issue of Oct. 26 (p. 611). The authors demonstrated that a clinical picture of nicotinamide deficiency, associated with a diminution of nicotinamide methochloride output, might follow the oral ingestion of a few thousand units of penicillin daily for several days in a subject who was apparently rather sensitive to dietary nicotinamide deficiency. These workers concluded that the penicillin swallowed by their subject had inhibited the metabolism of intestinal flora and diminished the quantity of the vitamin usually available from this source.

That this may not be the whole story of "penicillin stomatitis" is suggested by the following two considerations: (1) Whether in the ordinary way penicillin derived from sucking pastilles would be likely to reach the colon in sufficient quantity. (There is evidence that little penicillin enters the intestine from the blood-stream—e.g., McDermott *et al.* (1946)—and so we may take it that the drug must reach the colon via the small intestine.) Supposing a 500-unit pastille is dissolved in the mouth in fifteen minutes: 2,000 units an hour are slowly swallowed or absorbed from the buccal membranes. Of that portion which reaches the small intestine a further fraction will be absorbed (Abraham *et al.*, 1941; Florey and Florey, 1943). This appears to occur mainly from the duodenum (McDermott *et al., loc. cit.*). This small dose would probably be insufficient to give demonstrable blood levels, from the evidence of Burk, Ross, and Strauss (1945), McDermott *et al.* (1945), Krantz, Evans, and McAlpine (1945), the evidence assembled in a recent editorial in the *Lancet*, and other work.

The recent work of McDermott and his colleagues (*loc. cit.* 1946), quoted by Ellinger and Shattock, emphasizes the irregularity with which ingested penicillin is absorbed from or retained in the small intestine. Of two subjects who had received oral penicillin in a single dose of 5 million units, apparently in aqueous solution, the stools of one were found to contain 0.94 units of penicillin per gramme of stool, and of the other 1,200 units per gramme. In another subject, who took 100,000 units orally in water at two-hourly intervals for a twenty-four-hour period, the stool (held till the end of the experiment) contained no demonstrable penicillin. It is clear that the doses with which these authors worked far exceed the quantity one would swallow from sucking pastilles through a day, where ten or twenty probably represent as many as most patients would take.

(2) Whether the triad of sore tongue, sore mouth, and sores at the angles of the lips, which *may* be due to vitamin deficiency, could receive another explanation in these particular circumstances. Unfortunately most of the clinical work on oral penicillin has been limited to gonorrhoea, where the total dose is usually given inside of one day, but in this connexion it is perhaps worth noticing that in the very careful paper by Bushby and Harkness (1946), a subsection, "Toxic Manifestations," does not mention this particular complication. Florey and Florey (1943) treated a case of right orbital cellulitis with 60,000 units daily for seven days by capsules and duodenal tube, and a case of sensitive actinomycosis with 80,000 units daily for six days by duodenal tube, and do not mention that either case developed stomatitis or glossitis, although the second case (whose primary disease was unrelieved) developed coryza and gastro-intestinal disturbance.

It seems to me that Dr. T. V. Cooper is on the right lines when he suggests that the commercial lozenge base may be at fault. Until we have work of the quality of that of Ellinger and Shattock supplemented by readings of penicillin blood levels, gut levels from a Miller-Abbott intestinal tube (with its tip positioned by contrast fluoroscopy to be in the region of the ileo-caecal valve), and perhaps by urinary and stool penicillin levels, and by stool culture, I feel we may continue to use oral penicillin for oral infections, but that we should order lozenges made with agar or gelatin (as has Dr. Cooper) until it has been shown that the base alone and the heat-inactivated pastilles are not the cause of the stomatitis.—I am, etc.,

London, S.W.19. G. I. C. INGRAM.

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Epidemic Gastro-enteritis

SIR,—Having heard on the wireless and read in the newspapers about the outbreak of an epidemic of gastro-enteritis among maternity patients and newborn babies, I would like to mention how similar cases have been treated successfully by myself both abroad and here in Dorking County Hospital. It is the treatment which was used in the Berlin City Orphanage by Prof. Finkelstein and L. F. Mayer.

The aim of the treatment is to prevent dehydration and make the patient afebrile. It starts with a short period of starvation, during which only weak cold tea sweetened with saccharin is given. (1) 1 dr. (3.5 ml.) is given every 5 minutes until vomiting has ceased for about 1–2 hours. (2) Tea is gradually increased (cold or warm) for no longer than another 8–12 hours. (3) Expressed breast milk is then given—12 g. 2-hourly for 24 hours, and increased daily by 10 g. until the 5th or 6th day. (4) 3-hourly feeds are then given, the amount required according to age and body weight.

As the mothers are ill also, I would advise sterilizing the expressed breast milk. If breast milk is not available buttermilk may be used. Unfortunately reliable brands of buttermilk are not always available, but it can be obtained by using the milk left over from making butter from sweet cream. This milk should be boiled with 1% flour and 3% sugar.—I am, etc.,

Dorking. K. BRANDL.

Cerebral Malaria in Great Britain

SIR,—Drs. J. B. Ryder and R. T. Towson (Nov. 30, p. 815) state that in the literature they have only found two cases of cerebral malaria in Great Britain recorded. In the *British Medical Journal*, 1930, **1**, 336, I reported the case of a gentleman aged 35 who had just returned from West Africa. He had a rigor for which he took 10 gr. (0.65 g.) of quinine. Instead of being better the next day he had a very severe headache, and his temperature was still up. He called in a doctor who prescribed more quinine without effect. The headache became worse and worse, and vomiting set in. That night he was very delirious, with intense headache and frequent vomiting. Morphine gave him no relief. In the morning I was asked to see him as a case of meningitis. He was then semi-conscious, with a temperature of 103.6° F. (39.8° C.), pulse 112. His head was retracted and could not be moved forward. There was double Kernig's sign, and the toe reflexes were extensor. The abdomen was retracted, the spleen could just be felt below the ribs, and the liver was slightly enlarged. Some of the vomit during the night had been of coffee-grounds character.

I came to the conclusion that the case was probably one of cerebral malaria, and had 10 gr. of quinine hydrobromate injected into the buttock, and another 10 gr. into the other buttock in two hours, and another injection in four hours. Soon after this the patient became perfectly conscious and free from headache and vomiting. He was given an intramuscular injection of 10 gr. twice a day for the next three days, and had then quite recovered. This case illustrated the fact that quinine by the mouth is no good in cerebral malaria.

Since then I have seen post portem a child of 2 who had returned from India, where she had had malaria. She was taken ill one morning about 8.30 with headache, had a rigor with a temperature of 104° F. (40° C.), and became comatose at midday; she died at 4 in the afternoon. Malarial parasites were found in the blood after death.—I am, etc.,

Henfield. WALTER BROADBENT.

Dental Anaesthesia after Coronary Thrombosis

SIR,—Like Dr. F. Barnett Mallinson (Dec. 14, p. 921), and I am sure many others, I could not agree with your correspondent that a person recovering from a coronary thrombosis was a normal anaesthetic risk. Dr. Mallinson has suggested treatment which should ensure the patient against any mishap or untoward occurrence, and I doubt if safer treatment could be suggested. However, I venture to point out that it is most unlikely that a hospital patient would be afforded the opportunity to have teeth extracted a few at a time in this way, and so a different régime must be laid down as a routine treatment of a not uncommon condition.

The requirements during this anaesthetic are that the patient should be well oxygenated at all times, that the anaesthetic should be smooth, and of course that the required plane of anaesthesia should be reached but not passed. In your issue of June 17, 1945, I mentioned a technique that I had used considerably on very bad risk cases with complete success. This is quite applicable to out-patient dentistry and, I consider, very suitable for the case in point. No sedative premedication is given, though atropine sulphate 1/100 gr. (0.65 mg.) is probably indicated. With the patient in the dental chair a syringe of 5% "pentothal" (thiopentone) is strapped to the arm after the needle has been introduced into a vein. Before any "pentothal" is given the nosepiece of a gas and oxygen apparatus is applied to the face while 100% oxygen is run through the machine. Only when the patient is breathing this smoothly is the "pentothal" run in. This is given slowly, speed depending on the severity of the risk, but the respiration must not be allowed to get shallow, and so the patient will remain a good colour. When unconsciousness has supervened the gaseous mixture is altered so that the oxygen percentage is reduced and replaced by nitrous oxide. With a bad risk this must not go below 50% at first, and some lose their full pink colour at this stage. Others, such as the convalescent coronary case, will rapidly tolerate 25% or 20% oxygen. Further injections of "pentothal" or alteration of the gaseous mixture are made as and when required, but it must be realized that it is better to give more "pentothal" than to cause any degree of cyanosis. With out-patients the minimum of "pentothal" will be given, and so the maximum use will be made of the nitrous oxide, consistent with the patient remaining a good colour. With in-patients this is less important, but it must be remembered that as a group they are a different type of case. In this way a few dental extractions can be made after only 3–5 ml. of "pentothal."

Speed during the preliminary stages of the anaesthetic should not be aimed at. The safety of the patient is the only thing

that matters, and speed may well lessen this. Once they have reached the stage of surgical anaesthesia by this gradual process, very gravely ill patients will stand a prolonged anaesthetic very well provided there is no need to take them into the deeper planes. Frequently I have seen their blood pressure rise appreciably during 60 to 90 minutes of such anaesthesia.

This régime requires no special skill and no special apparatus: it can even be done with foot cylinders providing oxygen is used. There is no need for an operating theatre or to admit the patient, and so I feel that it should be mentioned in the treatment of this and similar cases. I have used this technique now on so many bad risk cases, especially during the war, that I feel that anyone who is not on the point of death can be taken to the first plane of the third stage with safety; and when I heard a few days ago at the anaesthetic section of the R.S.M. of a grave risk case that did not survive a 1 ml. dose of "pentothal" I came away feeling that had oxygen been given first the result might well have been different.—I am, etc.,

Emsworth. H. B. C. SANDIFORD.

Postgraduate Education

SIR,—I was pleased to read the letter of Dr. J. Maclean Smith (Dec. 14, p. 921) in which he pays tribute both to the warm welcome which was extended to the medical officers of the British Pacific Fleet by our colleagues in Australia and to the postgraduate educational opportunities provided out there. I have no doubt that there are many others who, like Dr. Smith, are grateful for having had experience of such postgraduate instruction. While in Australia as surgical consultant to the B.P.F. I was invited to become a member of the Postgraduate Committee on Medical Education of the University of Sydney and was able to attend a number of meetings at which the excellent work being done for postgraduate education by this committee became very apparent to me.

The correspondence tuition to which Dr. Smith refers was conducted by senior members of the teaching staff, who devoted much care and attention to it, and was supplied to medical officers away on service stations such as New Guinea and the Pacific Islands. It was much appreciated and is an idea which might well be given consideration here. Many medical officers from this country on far-away stations have adequate enthusiasm and much time on their hands and would no doubt welcome something like the Sydney correspondence courses. In Melbourne and Sydney, and indeed throughout Australia and New Zealand, postgraduate medical education has reached a high standard of efficiency. I should like to take this opportunity of again expressing thanks to our colleagues in Australia and New Zealand for all their kindness to those of us, who were out there with the Fleet, and in joining with Dr. Smith in hoping that friendly postgraduate teaching within the British Commonwealth will long continue and progress.—I am, etc.,

Cardiff. LAMBERT ROGERS.

Venereal Disease Control

SIR,—I read with rising alarm the article (Nov. 30, p. 825) by Lieut.-Col. R. R. Willcox on "Some American Ideas on Venereal Disease Control." I could not help feeling that this eminent venereologist viewed these American methods favourably, and was, without saying so explicitly, seeking to further them in this country. As a medical officer of health I am naturally anxious to secure that transmissible diseases are kept under control by all reasonable methods, but I think that there is a general tendency at the present time to lose sight of wider ethical considerations in trying to achieve immediate administrative results. Interference with the liberty of the subject can scarcely be too much curtailed, and the idea of compulsory investigation for venereal disease before marriage cannot, I think, be too strongly deprecated.

Even the risk that a relatively small number of people may infect others with a dangerous complaint should not be allowed to stampede us into further restrictions upon civil liberty, particularly at a time when the profession as a whole is trying to maintain its freedom against those who desire to enslave us, for the sake of perfectly laudable immediate results.—I am, etc.,

Weston-super-Mare. CYRIL G. EASTWOOD.

Errors in Diagnosis

SIR,—During the last six months I have had no fewer than four cases in which diagnosis of anxiety neurosis and nervous dyspepsia had been made, and which turned out to be (1) gastric ulcer, (2) carcinoma of stomach, (3) carcinoma of stomach, (4) advanced pulmonary tuberculosis. All these cases had been attending hospitals over a period of some years.

My contention in writing this letter is that too much attention seems to be paid to patients' neurotic symptoms rather than to seeking some organic cause. The diagnosis of nervous dyspepsia or anxiety neurosis is too easily made. Further investigation—*x*-ray examination—should, I feel, be made in all cases complaining of dyspepsia to exclude new growth. I have for some years now made it a rule that any patient complaining of dyspepsia for more than four weeks should go to hospital for *x*-ray investigation.—I am, etc.,

Willesden. L. SHELDON.

Treatment of Ingrowing Toenail

SIR,—I was rather surprised to see in the *Journal* of Oct. 19 (p. 589) Lieut.-Col. J. C. Leedham-Green's letter recommending as a simple and most satisfactory procedure that old-fashioned method of paring the nail with a piece of glass. Anyone who will try it will agree that it is a most tedious and unsatisfactory procedure. Years ago (in 1914) an American surgeon described a new method which is so simple that any doctor can easily do it under local anaesthesia, and the result is excellent and permanent. He pointed out that "ingrowing" is a misnomer, as the nail does not start growing sideways. What happens is that the toe, irritated by the pressure of the shoe against the edge of the nail, gets bigger, as anyone can see, so that often the nail gets partly embedded in the toe.

The logical thing to do is at the same time the simplest and best. A good wedge should be cut out of the side of the toe, cutting right down to the bone. The inflamed edge near the nail is left severely alone, but not so much should be cut out that the edges of the wound cannot be brought together without tension. A little 1% "novocain" is all that is required for anaesthesia. Two or three stitches and a gentle pressure bandage complete the simple operation. Sufficient tissue should be cut away that the nail may again rest comfortably on top of the nail bed instead of seeming to grow into it. A few days in bed is advisable for rapid healing.

The relief is wonderful and the result as a rule permanent if the operation has been performed *lege artis*, but if not enough flesh has been removed it is quite easy to remove some more at a second sitting, and sometimes the inside may be treated as well in the same way till a nice small toe is obtained protected by the nail as intended by nature. It is really surprising that this operation is not yet being universally taught, as it is so logical, simple, and effective.—I am, etc.,

Rustenburg, Transvaal. S. J. D. ESSER.

Advertising Patent Medicines

SIR,—In the *Journal* of Dec. 7 (*Supplement*, p. 150) the report of a debate by the Hunterian Society quoted one doctor as stating that £90 million a year was spent on the advertising of "patent medicines." In the recently published report, *Statistics of Advertising*, which was based upon inquiries carried out by the National Institute of Economic and Social Research on the initiative of this Association, the figure of expenditure by manufacturers on the advertising of patent and proprietary medicines, tonic wines, and rupture appliances in 1935 was £4,822,000, almost exactly the figure which Mr. Mortimer quoted for 1938 in respect of the Press only. The Institute's computation, however, comprises Press, outdoor, and radio advertising and represents 7.4% of total advertising expenditure directed to the final consumer in that year. It should be noted, moreover, that the medicines, etc., the advertising of which represented £4.8 millions excluded all products where the ratio of advertising cost to sales was under 3%. In computing these figures the Institute has indicated the possibility of considerable margins of error, of the order of 10% to 20%.

The Advertising Association is now planning to collect systematic statistics, *inter alia*, in relation to proprietary advertising. One object will be to eliminate the considerable margin

of error which may exist in the figures for particular categories, such as patent medicines and toilet preparations. The statistical investigation recently concluded provides a most useful starting point to a continuous statistical system. Meanwhile, deductions from the present figures should be drawn with caution. It would be fair to add that the fact of a proportion of advertising expenditure of 25% or more in relation to sales is by itself no measure of the relative merits or demerits of the preparations advertised. The great bulk of this type of advertising is subject to a considerable measure of supervision in one way or another, but the Association and its affiliated bodies recognize that the existing standards of restraint require to be made more explicit, more concise, and more uniform. We believe we are making progress to that end with the general support of professional bodies, such as the British Medical Association, who have been consulted.—I am, etc.,

London, E.C.4. J. L. HENDERSON, Director and General Secretary, Advertising Association.

Amenorrhoea during Internment

SIR,—I have just read Dr. Annie Sydenham's article (Aug. 3, p. 159) on "Amenorrhoea at Stanley Camp, Hongkong, during Internment." It is interesting to recall a somewhat similar condition when the Japanese first occupied Ipoh, seven weeks before the fall of Singapore. In spite of the chaos I was able to see about 30 cases of amenorrhoea, especially among young unmarried girls. There were then numerous cases of rape and conditions were most uncertain. Food, however, was not so very difficult to get owing to stocks left over by the British. Nearly all the cases started menstruating again without any treatment after 4–5 months, when conditions were slightly more settled. I would put the cause of all these cases to emotional shock.—I am, etc.,

Ipoh. GOH TEIK WAH.

Pay of Pathologists and Bacteriologists

SIR,—I very much regret that my letter provoked the thought that I consider a specialist to be of higher prestige than the G.P.—at least, this would appear to be the case on reading Dr. G. Behr's letter (Dec. 14, p. 919). Having been a G.P. myself I can assure Dr. Behr that in my opinion there is no higher prestige than that of the family practitioner's, which, however, does not alter my contention that the present salaries paid to pathologists and bacteriologists are little short of outrageous.

If a G.P. earns, say, £1,500 per year (and a doctor is capable of doing so within a year or two of qualification), then the pathological specialist should be paid accordingly—i.e., a similar sum. I do not think this unreasonably "rebellious." I hold no brief for a salaried medical service, but sometimes I wonder if such a service is the only means by which the "junior" pathologist will be freed from a most unjust system of remuneration.—I am, etc.,

LABORATORY DOCTOR.

Diet and Canine Hysteria

SIR,—Allow me to congratulate you on the publication of Sir Edward Mellanby's article (Dec. 14, p. 885) and your excellent leading article thereon (p. 903). For some years now the veterinary profession have realized the importance of a toxic substance or toxic combination in diet as being a direct and positive cause of specific hysteria, so-called Fright's disease, or "running fits," and Sir Edward's contribution has gone a long way to narrowing down the possible causes. As you indicate, the next step is to study the result of feeding agenized wheat gluten to dogs, and, if this fails to produce the disease, then to study the effect of the agene process on all or part of the vitamin B complex.

M. B. Richards, in the *British Medical Journal* (1945, **1**, 433), describes a pyridoxine deficiency in suckling rats whose dams had received a high aneurine content. In *Nature* (1946, **158**, 306) she records that in the experiment described above she observed but did not report that fits were not manifested in litters where does received national wheatmeal flour 85% extraction instead of white flour. I understand that in this part of the country during the war it has not been normal practice to apply the agene or any bleaching or improving process to flours of high extraction rate, and it is possible that Mellanby's work would throw fresh light on Richards's experiment.

By the same token the next interesting step would be to feed pyridoxine with diets known to be capable of producing hysteria, and if this prevents the disease the problem will be further elucidated. The veterinary profession has known for a long time that certain batches of dog food are capable of producing hysteria, and I have access at the moment to a bag of dog food which will produce hysteria in less than a week from the time feeding is commenced. I have had some pyridoxine on order for some months, which I hope to receive shortly, and propose using it as a therapeutic on dogs fed on a known hysteria-producing diet. Mellanby's article indicated that rats were not affected, but it may well be that the hysteria syndrome is only manifested in adult rats when the toxic factor is present in large quantities, and small quantities can only be demonstrated in suckling rats whose dams have been fed on a hysteria-producing diet.

With regard to the human aspect of the problem I do not think the new facts necessarily present a grave problem, as there is no doubt that pre-war experience demonstrated that the toxic factor was much greater in dog biscuits than in bread—even white bread—as evidenced by observation of kennels of dogs fed on both these diets. On the contrary, I have frequently seen hysteria developing in kennels where ship's biscuits (emergency lifeboat rations) were fed, and I have, very infrequently, seen hysteria follow feeding with "brown bread." Any complete set of experiments would require to take into account the high temperatures associated with baking.

Sir Edward's description of the fits is excellent, and it is a matter of some importance that in specific hysteria the dog's nervous condition is not normal between fits. I would like to issue a word of warning here. In the past, as indicated in the article, a multiplicity of causes were implicated as being responsible for hysteria, and this was not without some reason. Conceding that specific hysteria occurs as described and is caused by a toxic factor in food, it *must* be recognized that hysterical attacks, clinically indistinguishable from those described, do occur due to the virus of distemper in dogs that have had no hysteria-producing foods. In the past two years outbreaks of distemper of a very virulent type have frequently been ushered in by typical hysteria, to be followed later by the more common distemper symptoms. It may be that the virus creates a set of circumstances whereby larger quantities of an accessory food factor are required than is normal, analogous to the increased demand for biotin in rats given avidin.

Another interesting feature whereby a virus appears to have an antivitamin effect occurs in distemper in puppies between the ages of 2 and 4 months. Such animals develop the condition described by May Mellanby as dental hypoplasia, even while large quantities of vitamin D are given during the disease. Mellanby produced this condition in the disease-free puppies by diets deficient in D, and it might be that in distemper there is a failure to assimilate D because of associated bowel catarrh. Or, again, it may be that the requirements are greatly increased by the action of the pathogenic agent. I have tried the effect of radiation by ultra-violet light in such cases, but in practice there are difficulties in carrying this out and results have been inconclusive. The question could be readily solved by the experimental method. An investigation of such altered vitamin requirements would probably indicate the way to their more rational therapeutic use.—I am, etc.,

Glasgow. WM. L. WEIPERS.

Dr. George Gunn, *M.B.E.*, F.R.C.S., of Crowborough, Sussex, who died on April 3, 1946, left £10,189. Dr. W. S. A. Griffith, *C.B.E.*, F.R.C.P., F.R.C.S., of Haslemere, Surrey, who died on Feb. 26, 1946, left £79,989. After various legacies he bequeathed one-third of the remainder to St. Bartholomew's Hospital for the development of the obstetrical and gynaecological department to perpetuate the name of Dr. Matthews Duncan, and one-third to the medical college. Dr. Howard Henry, *M.C.*, M.D., of Debenham, Suffolk, who died on June 24, 1946, left £14,564. Dr. A. B. Murray, of Banff, who died on Oct. 13, 1946, left personal estate in England and Scotland valued at £45,850.

Obituary

Dr. DORIS MARY RINGROSE died at West Park, Leeds, on Nov. 7 at the age of 46. She was educated at George Watson's Ladies' College, Edinburgh, and graduated M.B., Ch.B. at Edinburgh University in 1923, taking the D.P.H. the following year. She worked in general practice until 1926, when she settled in Leeds and married Mr. H. T. Ringrose, the pioneer of automatic firedamp alarms in mines. The principle of this device has recently been applied to the continuous indication of anaesthetic vapour concentrations. In 1930 Dr. Ringrose resumed her medical work, and until her illness was employed by the West Riding County Council and the Batley Corporation on antenatal and child welfare work. During the war she served on a medical board for recruitment to the women's Services. She also took a great interest in industrial medicine. She was a woman of truly high ideals, of great kindliness of heart, and she was a very loyal friend. Her death came as a great shock to all those who knew her, and she will be greatly missed. She leaves a daughter who is still at school, and a son now studying medicine at Cambridge.—H. F. H.

Dr. GEORGE LOCKE, of Hastings, died in retirement at Sedlescombe, on Nov. 19, at the age of 93. A native of Aylesbury, Dr. Locke qualified L.R.C.P.Ed. in 1881, took the L.S.A. in the same year, and the M.R.C.S. in 1886. He spent his early years in general practice in Princes Risborough and later in London. In 1893 he settled at Hastings, where he practised until his retirement in 1930. A man of wide interests, Dr. Locke took a keen and energetic part in local affairs. He was appointed a Justice of the Peace in 1906 and sat regularly on the Hastings Bench until shortly before the war. He was also vice-chairman of the old school board and chairman of the local branch of the Royal Surgical Aid Society, a post he held for many years. His greatest pleasure and interest was in the St. John Ambulance Brigade, which owes him a deep debt of gratitude for his devotion to its development. For his part in this work he was made a Commander of the Order of the Hospital of St. John of Jerusalem, an honour of which he was justly proud. Dr. Locke was a member of the British Medical Association for forty years, and took a prominent part in the activities of the Hastings Division, which he represented at the Annual Representative Meetings in 1912, 1913, and 1921. He was president of the Sussex Branch in 1918. He was also an ex-president of the East Sussex Medico-Chirurgical Society. Dr. Locke is survived by a son and three daughters. Mrs. Locke died nineteen years ago, and his second son was killed in the first world war.

With the death of Dr. IZSET MEAD HAYTHORNTHWAITE at the age of 87 at King's Langley, Herts, on Nov. 24, one more link is severed with the days of women's emancipation, she, in 1886, being the second woman to receive the triple qualification of Edinburgh and Glasgow. Engaged by the Zenana Bible and Medical Mission, she took postgraduate training in Vienna in midwifery and diseases of the eyes and ears, attending, among others, the clinic of Prof. Politzer. In 1887 she was house-surgeon at the New Hospital for Women (which stood on the present site of Marylebone Station) under Dr. Elizabeth Garrett Anderson, and after that went to India. For five years she worked in the Lady Kinnaird Hospital for Women and Children with Miss Haskew (now Mrs. Birket), to whose efforts the building of that hospital was largely due. In 1892 she married the Rev. J. P. Haythornthwaite and this, with a trip to New Zealand, put a term to regular medical work; but while in Agra, 1893–1911, as wife of the Principal of St. John's College, she found ample opportunity to minister to the families of missionaries as well as having five children of her own. In 1915 her eldest son was killed in action in France and she, though by now getting old, somewhat infirm, and suffering from the disability of a malunited fracture of the wrist, and running a home with little help, did her best to fill a place in the depleted ranks of doctors serving the civilian population. During 1915–18 she filled the posts of clinical assistant at the Garrett Anderson Hospital for three months, six months as resident medical officer at the Nayland Sanatorium, filled a short gap at the Rosa Morrison Home of Recovery at Barnet, was for three years visiting physician at the Four Boroughs maternity clinic, and first doctor to the King's Langley antenatal clinic. Predeceased by her husband by many years, she leaves three children, two of them doctors in India, who mourn the loss of a personality of more than ordinary character, ability, and sweetness.

Dr. WILLIAM MURRAY, who died at Hessle on Nov. 29, was a native of Montrose; he studied in the University of Edinburgh, graduated in 1891, and took the M.D. in 1895. After being house-surgeon at Tottenham Hospital, he went to sea for three years in the service of the P. & O., and then came to Hessle in partnership with the late Dr. Fraser, whom he later succeeded. He was a member of the Hull Medical Society and of the B.M.A. from 1895 till the day of his death, being chairman of the East Yorkshire Division in 1924–25. For many years he was honorary medical officer to the Hull Seamen's and General Orphanage and devoted much time and thought to the interests of that charity and to the well-being of the children. In 1903 he joined the Territorial Army and reached the rank of lieut.-colonel in the 2nd Northumbrian Brigade, R.F.A. He was officer in charge of the Central Hospital in Hull until it was closed down. Dr. Murray retired from practice in 1937, but on the outbreak of war again interested himself in lecturing to the St. John's Ambulance and in other professional activities. He will be greatly missed by a host of ex-patients and personal friends in Hessle and the surrounding district. Everyone admired his wide learning, his phenomenal memory, and his powers as a raconteur, but perhaps his most endearing characteristics were his unfailing cheerfulness and his keenness while at work or play. He was a good horseman, a pioneer motorist, and a fisherman to whom the mysteries of flies and fish were an open book.

Dr. ROBERT LEE MOORE, J.P., died at his home in Bangor on Nov. 30. For over half a century Dr. Moore carried on an extensive practice in Bangor. He was a skilful family doctor with a real interest in the welfare of his patients. A native of Belfast, he was educated at the Royal Belfast Academical Institution and at Liverpool, qualifying in 1890. He was closely associated with the Bangor Hospital from its beginning as a small cottage hospital, and was a life governor of the present hospital. He had an inexhaustible fund of stories about old Bangor personalities and events, and he was an authority on County Down folklore and dialect. In his youth Dr. Moore was a noted Association football player and athlete, and throughout his long life his love of sport continued. He was a member of the Royal Ulster Yacht Club and a life member of Bangor Golf Club. A prominent and highly esteemed figure in the Masonic Order, he occupied most of its important offices. He is survived by his wife, three daughters, and two sons, one of whom is Dr. B. P. L. Moore, clinical pathologist to the Mater Hospital, Belfast. A third son died in Java while a prisoner of war in Japanese hands.

Dr. GEORGE STEWART CLARK, of Edinburgh, who died on Dec. 17, had been school medical officer for Midlothian and Peebles from 1924 until his retirement early this year. He had previously held a similar post at Roxburgh for four years. Dr. Clark graduated at Edinburgh University, and was for two years assistant medical officer at the Edinburgh City Hospital. For six months he was junior assistant to the Professor of Public Health, Edinburgh University, and for one year senior assistant medical officer at Monsall Hospital, Manchester. He worked under the Edinburgh education authority for nearly eleven years as assistant medical officer, and had served for four years with the R.A.M.C. Dr. Clark, who was 72 years of age, is survived by his widow and a son and daughter.

Dr. JOHN FLASBY LAWRANCE WHITTINGDALE, the doyen of the medical profession in Dorset, died on Dec. 11. It is given to few men to have so many years of life and so many years of active professional work. Born at Thornton-in-Lonsdale on Oct. 6, 1858, he was educated at Richmond School and at Gonville and Caius, Cambridge. He qualified at Edinburgh in 1883, and became house-surgeon to Prof. John Chiene, and afterwards to Sir Halliday Croome at the Lying-in Hospital. He did two trips as surgeon to the P. & O. Company, being shipwrecked off Trincomalee. After a year as assistant in Maidstone, Dr. Whittingdale came to Sherborne in 1889, where for fifty years he was actively engaged in one of the largest medical practices in the county. He held the appointments of public vaccinator and parish medical officer to two large districts, was medical officer to Sherborne School, to Sherborne School for Girls, the post office, and the almshouse. During the whole of his active life he was surgeon to the Yeatman Hospital, and on his retirement was elected consulting surgeon and vice-president of the hospital. For fifty years he was a mainstay of the Dorset Division of the B.M.A., regularly attending all meetings. He held all the offices in succession, both in the Division and in the Branch. From 1914–18 he was Chairman of the Local Medical War Committee and occupied this position in the early days of the recent war until ill-health

compelled him to retire. He was at one time much occupied in local affairs and served as chairman of the Sherborne U.D.C. Interested in apiculture he was for many years chairman of the local beekeepers' association. A lifelong devotion to field sports occupied his scanty leisure. He was lamed permanently by a hunting accident in 1896, but shot and fished until his eightieth year and had a profound knowledge of game birds and fishes. It is remarkable that a man so fully occupied with medical practice in a wide district could still manage to be interested in and find the time for so many other activities. He will be greatly missed in Sherborne and by the profession in Dorset.

The late Dr. HARRY ATKIN DUNKERLEY was born on Dec. 26, 1883, son of John Whiteley Dunkerley, L.D.S., a founder of the Manchester Dental Hospital. Educated at the Central High School and Victoria University, Manchester, he graduated M.B., Ch.B. in 1912. As a student, being unable to take part in outdoor sports, he took keen interest in the R.A.M.C.V., and was in the 2nd Western General Hospital, reaching the rank of staff sergeant, R.A.M.C.T. After four years as a colliery surgeon he returned to Manchester in 1917 and was in practice there for 22 years. Glaucoma in 1925 resulted in blindness of the left eye; he also had myopia to a high degree. Progressive myopia and large scotomatous areas in the visual field of the right eye eventually made it impossible to discharge professional duties efficiently, and through help from the National Insurance Defence Trust he was enabled to retire in 1939 after an overwhelming struggle against affliction in later years of active professional life.

Dr. VIKTOR POLLAK, who died suddenly on May 7 this year, was born at Rokicany, Austria-Hungary, on March 18, 1884. After his schooling in Prague he entered the University there, graduating M.D. in 1908. The following six years he spent in hospital appointments in Prague, Vienna, and in the Austrian Army. He was assistant to such famous men as Yaksch, Schauter, and Knöpfelmacher. Immediately before the first European war he was working with Wertheim. He was surgeon in the Austro-Hungarian Army throughout the 1914–18 war, serving with distinction on the Russian and Italian fronts. After the war he set up in private practice in Vienna, largely among women and children. After twenty years' busy and valued work he had to flee his beloved Vienna in 1938, to find refuge first in Prague, then in England. For the last four years he held a responsible post on the staff of the North Middlesex Hospital. A colleague writes: It is remarkable what a warm place Viktor Pollak won in all our hearts. How bravely he faced the difficulties of new work in a strange land—difficulties which would have daunted many a younger man. To say he adapted himself to his new work would not be accurate—he did up to a point, and then all around him joyfully adapted *their* ways to his. His English was emphatic and picturesque and well became his distinguished, rather military bearing. He was, by the way, very proud of his soldiering in those far-off days before the first war, in the old Austro-Hungarian Army. He often looked back wistfully to the old empire. It was good to hear him talk of the medical giants of Vienna—he had worked with men who knew them all—Billroth, Czerny, Mikulicz. Pollak took a great pride in his work—many a time he was chaffed in the mess about some diagnosis only to be vindicated in the operating theatre or post-mortem room. His accurate clinical accounts were often embellished by the most excellent sketches of the condition found; these rapid, vivid drawings were the envy and joy of his colleagues. He died as he would wish, in harness, with no warning, having won the love and admiration of all who worked with him.

We report with regret the sudden death on Aug. 19, at Montego Bay, Jamaica, of Dr. EUGENE DE MONTEVIN GIDEON, formerly M.O.H. of St. James, a position he recently relinquished to become medical superintendent of West Indies Sugar Estates, Ltd., a division of Tate and Lyle, Ltd. Born in 1885, he was educated at Bedford Grammar School and at Toronto University, graduating M.B. with honours in 1907. Returning to England he took postgraduate courses at the London and at the Queen Charlotte Hospital, obtaining the M.R.C.S., L.R.C.P. in 1908. After a few years in private practice he entered the Jamaica Medical Service and was medical officer of the Buff Bay district for many years. During this period he was selected by the Government to represent Jamaica at the British West Indies Medical Conference at Georgetown, British Guiana, in 1921. He practised in partnership with his brother, Dr. Cyril Gideon, in Kingston for a short time, and acted as M.O.H. for the Kingston and St. Andrew Corporation before taking up his duties at Montego Bay. Eugene Gideon joined the B.M.A. in 1909 soon after qualifying and was an active member up to the time of his death. He held office as a member of council from 1932–9, was chairman of the obstetric section, and was elected president of the branch in 1934. By his wise counsel, his tact, and his felicity of speech he rendered invaluable service to the Association, and did much to bring about happy solutions of the many problems which the local branch had to face in its dealings with the Government. His presidential address on "Fraternity in Medicine" was an appeal to the members to improve social and professional relations, and with his charming manner and engaging personality he was himself a brilliant example of the precepts he advocated in this respect. He was seen perhaps at his best when he presided at a dinner given in honour of the late Lord Moynihan in 1935, and in the same year at a reception for the visiting members of the Pan-American Medical Association. He did splendid work, too, when the then General Secretary, the late Dr. G. C. Anderson, visited Jamaica in 1939. Dr. Gideon was a man of outstanding professional ability, loyal to the profession which he loved, and sympathetic always to his colleagues and friends. The medical profession and, indeed, the whole island have suffered a great loss by his death.—G. I. L.

Wing-Cmdr. H. M. Stanley Turner writes: It was with deep regret that I heard of T. S. RIPPON'S death (Dec. 14, p. 922). We were associated for many years, and he was one of my officers in the Middle East. He has a unique claim to fame in that he must undoubtedly be regarded as the father of the Royal Air Force Medical Branch. At the time the Royal Air Force was constituted as a separate Service in 1918 the question arose as to whether it should or should not have its own separate medical service. It was Rippon who made out an overwhelming case for a separate medical service, and the subsequent history of the R.A.F. Medical Branch has fully justified this claim, both in the intervening period between the two wars and especially in the war recently ended. Rippon had a very shrewd, scientific mind which foresaw clearly the highly specialized work which a R.A.F. Medical Service would be called upon to undertake and the lines of research which, as the Service developed, must necessarily be followed. He was a delightful colleague with whom to work, with a quaint sense of humour which never failed even under the most adverse circumstances; and he is entitled to a niche as one of the pioneers in aeronautical medicine, a branch which even to-day is only in its infancy. Those of us who knew him well will always regard him with respect and affection.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

The following candidates have been approved at the examination indicated:

FINAL M.B.—*Part I* (*Surgery, Midwifery, and Gynaecology*): H. D. Alexander, P. S. Andrews, W. E. C. Astle, C. P. Atkin, A. P. C. Bacon, W. H. Barker, H. B. Barlow, J. G. Bennette, H. C. H. Bird, J. P. Bull, D. B. Cathcart, D. Cooper, H. W. Cornford, J. D. Cox, C. H. K. Daly, M. C. Edmond, J. B.-C. Evelegh, A. W. Ferguson, J. Fiddess, N. B. Finter, D. K. Ford, J. A. S. Forman, W. D. Foster, J. M. Frew, J. H. Garson, R. G. Gibbs, A. W. Halfhide, B. Hardie, M. Harington, R. E. D. Harvey-Samuel, C. W. Hollingsworth, D. A. P. Hunt, J. S. Jenkins, W. P. Kelly, N. Kennedy, C. C. Kenred Smith, H. B. Kidd, F. R. Lambert, T. C. Langdon, D. D. La Touche, D. N. Lawson, M. G. H. Lewis, J. E. MacIver, E. V. Mackay, K. M. McNicol, G. C. Manning, I. A. Marriott, R. Marshall, R. K. Mason, W. T. S. Moore, D. C. Morley, P. C. J. Nichol, T. G. Osmond, D. S. Paine, J. P. Paul, J. K. P. Perera, A. Pines, R. C. S. Pointon, A. I. D. Prentice, I. R. D. Proctor, R. H. B. Protheroe, P. K. Pybus, E. T. Roberts, R. H. C. Robins, A. W. Robinson, M. G. Rolfe, A. J. Russell, J. D. Scott, J. G. E. Shaw, E. Sherrah-Davies, E. P. H. Shortt, W. Spector, M. P. Spence, G. W. Sykes, N. Tate, K. C. G. Taylor, M. B. Thompson, P. G. Treharne, G. G. Walker, A. P. Waterson, J. D. Whitby, M. E. E. White, J. S. W. Whitehead. *Women:* J. M. Cockrell, J. Crossley, P. E. Davis, Mrs. B. M. Eley, L. A. Farquharson, A. D. Fuller, J. K. Goodacre, H. A. Jaques, I. Kane, Mrs. P. D. Kilner, R. M. Licence, Mrs. M. R. Simpson, S. G. Wills. *Part II* (*Principles and Practice of Physic, Pathology, and Pharmacology*): A. V. Adams, R. J. Alcock, M. S. Aldridge, T. W. Backhouse, A. P. Baker, C. P. Bennett, E. M. M. Besterman, D. A. L. Bowen, G. T. F. Braddock, D. C. Bradford, D. W. Burnford, A. O. Chase, J. M. Childs, P. W. S. Coghill, J. Crossley, A. J. Danby, E. B. Davies, G. H. P. Drake, E. H. Eason, R. D. Eastham, J. A. Elliott, P. A. Emerson, J. Fiddess, G. R. Freedman, J. H. H. Glyn, T. C. Hallinan, R. Hodgkinson, K. G. Irving, I. S. M. Jones, B. T. Kieft, J. G. Kilner, C. S. Kirkham, D. N. Lawson, M. H. Lessof, A. D. R. MacAuslan, J. A. McDonald, A. C. Mackay, J. McMillan, E. D. Marsh, H. E. S. Marshall, R. Marshall, J. G. Mathewson, D. G. Miller, R. H. B. Mills, J. J. Morland, K. S. Murray, A. G. Norman, D. O'Brien, T. C. L. Parry, F. G. Pattrick, A. Pines, E. Pringle, I. R. D. Proctor, G. Raperport, R. H. C. Robins, W. J. B. Rogers, J. F. F. Rooney, P. W. Rowsell, R. A. Ryan, D. Seymour, E. S. O. Smith, M. F. Smith, J. B. Steeds, J. P. Stephens, W. M. B. Strangeways, J. E. H. Stretton, A. D. Thomson, J. C. Ward, D. J. Watt, W. B. Webb, M. E. E. White, R. H. L. Wolfsohn. *Women:* Mrs. E. W. Higgens, G. F. Jacob, S. M. McNeile, N. J. Pease.

UNIVERSITY OF LONDON

The title of Professor Emeritus of Surgery in the University has been conferred on G. Grey Turner, LL.D., M.S., F.R.C.S., on his retirement from the Chair of Surgery, which he has held at the British Postgraduate Medical School since 1934.

The title of Professor Emeritus of Physics in the University has been conferred on Sydney Russ, D.Sc., on his retirement from the Joel Chair of Physics, which he has held at the Middlesex Hospital Medical School since 1920. He is succeeded in the Chair of Physics by J. E. Roberts, D.Sc., Ph.D.

Mrs. Meave Kenny, M.D., F.R.C.O.G., has been appointed to the University Readership in Obstetrics and Gynaecology tenable at the British Postgraduate Medical School from Oct. 1, 1946.

The following candidates have been approved at the examination indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN MEDICAL RADIOLOGY.—P. E. S. Palmer, G. W. Pimblett, M. P. Shapiro. *Part I:* V. Berman, E. B. Brennan, P. T. Chopping, J. M. Corall, P. M. Davies, J. Dawson, H. F. T. Deane, A. Greig, G. T. Holroyd, C. H. Kitchen, M. J. Meyer, R. O. Murray, D. H. Nelson, W. D. Nichol, J. H. O'Connell, R. H. Owen, B. Prasad, C. Stuart, P. Tettmar, A. Wolpowitz, M. C. Wood, W. B. Young.

UNIVERSITY OF MANCHESTER

The following candidates have been approved at the examination indicated:

FINAL M.B., CH.B.—Joan Hampson (second-class honours), C. J. T. Archer, Kathleen Burn, H. S. Coulsting, Dorothy R. Davies, Vera A. Dearden, O. G. Dodge, C. J. Glancy, A. B. Haward, J. B. Howard, S. T. Lunt, J. Needoff, E. L. Peel, N. W. Preston, Kathleen Rampling, A. E. Shelswell, Lorinda Wallace, Joan M. Waterfall. *Part I:* Sheila A. Costello, F. J. Davies, A. Kinsey, J. E. Parry, S. L. Royce, P. Wolf, K. S. Holt.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

The following Hunterian Lectures will be delivered at the College (Lincoln's Inn Fields, W.C.) on Thursdays at 5 p.m.: Jan. 9, Prof. J. B. Macalpine, "Growths of the Renal Pelvis and Ureter"; Jan. 16, Prof. R. H. Franklin, "Congenital Atresia of the Oesophagus"; Jan. 23, Prof. H. A. Haxton, "Regeneration after Sympathectomy, and its effects in Raynaud's Disease"; Jan. 30, Prof. John Howkins, "Movement of the Diaphragm after Operation." The lectures are open to those attending courses in the College and to all other medical practitioners and advanced students.

A course of lectures in ophthalmology will be held at the College and will be given as follows: Jan. 20, at 3.45 and 5 p.m.; Jan. 21, at 3.45 and 5 p.m.; Jan. 22, at 3.45 and 5 p.m.; Jan. 23, at 3.45 and 6.15 p.m.; Jan. 24, at 3.45 and 5 p.m.; Jan. 27, at 3.45 and 5 p.m. The fee for the whole course is £5 5s. Fellows and Members of the College and Licentiates in Dental Surgery will be admitted on payment of a fee of £3 3s. Applications, accompanied by a cheque for £5 5s. or £3 3s., should be sent to the assistant secretary, Royal College of Surgeons of England, Lincoln's Inn Fields, W.C.2.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

The annual meeting of the College was held on Dec. 5, when Dr. D. M. Lyon was re-elected President. Drs. W. D. D. Small, L. S. P. Davidson, J. D. S. Cameron, H. L. Wallace, I. G. W. Hill, and D. K. Henderson were elected to form the Council of the College for the ensuing year. Dr. W. D. D. Small was nominated Vice-President.

SOCIETY OF APOTHECARIES OF LONDON

At a recent meeting of the Court of Assistants with Dr. C. T. Parsons, Master, in the chair, the announcement of the death of Sir Walter Langdon-Brown, Honorary Freeman of the Society, was received with great regret. Dr. J. P. Hedley was reappointed as the Society's representative on the General Medical Council.

Common Hall was recently called to discuss the proposal to admit medical women to the Yeomanry and Livery of the Society. The result of the vote was reported to the court, which has decided that medical women shall be admitted.

The Diploma of Mastery of Midwifery was awarded by examination to J. G. Hunt.

The Diploma in Industrial Health was granted by examination to F. H. Tyrer and J. B. Lynch.

The Diploma of L.M.S.S.A. was granted upon examination to the following successful candidates: I. J. R. Musson, H. F. Goldman, H. M. Price, J. O. Kelsey, G. A. May, A. H. J. Whitehouse, H. Freeman, J. A. Sodipo, R. M. Holmes, T. C. McC. Gilmore, S. L. O. Jackson.

FACULTY OF RADIOLOGISTS

The following candidates have satisfied the Board at the recent examination for the Fellowship: R. J. Keating and G. Simon (Radiodiagnosis).

The Services

Lieut.-Gen. Sir W. P. MacArthur, K.C.B., D.S.O., O.B.E., retired pay, to be Colonel Commandant, R.A.M.C., in succession to Lieut.-Gen. Sir James Hartigan, K.C.B., C.M.G., D.S.O., retired pay, who attained the age limit for the appointment on that date.

Surg. Cmdr. R. H. Enoch, R.N.V.R., has been awarded the R.N.V.R. Officers' Decoration.

The following officers have been mentioned in dispatches in recognition of gallant and distinguished services in Malaya in 1942: Col. J. M. Mitchell, O.B.E., Lieut.-Col. L. T. Pearson, Lieut.-Col. (Temp.) W. J. L. Neal, O.B.E., M.C., Lieut-Cols. (Acting) E. G. Hardwood and W. G. Kennedy, Majors K. F. Alford and L. Feinhols, Major (Acting) S. G. Nardell, Capts. Arora, O. F. Campbell, A. K. Marwat, and A. Roy, and Assistant Surgeons R. R. Braganza and G. McG. G. Hartley, I.A.M.C.

Medical News

Dr. Innes Pearse will speak on the Peckham Health Centre at a meeting of the London Association of the Medical Women's Federation in the Hastings Hall of B.M.A. House on Tuesday, Jan. 7, at 8.30 p.m. The next meeting will be held on Wednesday, Feb. 5, when Miss D. J. Collier will speak on the influence of war experience on everyday ear and throat treatment.

A meeting of the Faculty of Homoeopathy will be held at the London Homoeopathic Hospital, Great Ormond Street, W.C., on Thursday, Jan. 9, at 5 p.m., when Dr. Tatiana Hardy will give an address on "Allergy."

The London Council of Social Service (7, Bayley Street, Bedford Square, W.C.1) has arranged a conference on "Special Forms of Catering for the Aged, Invalids, and Infirm," to be held at Bonnington Hotel, Southampton Row, W.C., on Saturday, Jan. 18, at 10.30 a.m., with Lord Amulree, M.D., F.R.C.P., in the chair.

The Central Office of Information (Montagu Mansions, Crawford Street, W.1) has designed an exhibition for the Ministry of Labour and National Service, the Ministry of Health, and the Ministry of Pensions entitled "And So To Work," which will be open on the exhibition site in Oxford Street, London, W., on weekdays from 11 a.m. to 7 p.m., from Jan. 8 to Feb. 1 inclusive. The exhibition will show the rehabilitation and resettlement of the disabled from hospital to training centre and so to work, and demonstrations will be given by physiotherapists, occupational therapists, and remedial gymnasts. Questions will be answered by experts at the information centre in the exhibition.

An Ethiopian Exhibition of arts and crafts, the first of its kind in England, will be held for a fortnight from Jan. 20, under the auspices of the Princess Tsahai Memorial Hospital Council at Foyle's Bookshop, Charing Cross Road, W.C.2. Lectures on the Ethiopian language, literature, Church, etc., will be given; the exhibits will include specimens of the fine and applied arts, photographs, and children's drawings. The committee would be grateful for the loan of further exhibits.

A meeting of the Association of Industrial Medical Officers will be held at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C., on Friday, Jan. 24, at 4 p.m. At 5 p.m. on the same day there will be a joint meeting with the School Medical Service Group of the Society of Medical Officers of Health, when the subject for discussion will be "The Change from School to Industry," to be opened by Drs. A. A. E. Newth and T. A. Lloyd Davies. On Saturday, Jan. 25, at 10.30 a.m., Mr. R. H. Young will give an address on "The Diagnosis, Pathology, and Treatment of Intervertebral Disks," illustrated by a colour film.

Messrs. Boots have endowed for seven years a research fellowship of £1,000 per annum at St. Mary's Hospital. The board of management of the hospital and the council of the inoculation department have elected R. E. B. Hudson, M.B., B.S., to be the first Boots' Research Fellow.

Messrs. Burroughs Wellcome and Co. announce the adoption of a five-day week for their London offices and warehouse. Until further notice an emergency staff will be in attendance on Saturday mornings at 12, Red Lion Square, W.C.1 (Tel.: Chancery 6621), from 9 a.m. to 12.30 p.m., to deal with urgent orders.

Mr. Joseph Cunning, F.R.C.S., F.R.A.C.S., and his wife, Mrs. Annie Broomhall Cunning, M.B., have given the house and grounds of Broome Park, Betchworth, Surrey, to the Electrical Industries Benevolent Association as a home for old people, to serve as a memorial to their son, James Erskine Cunning, who was killed in a raid over Essen in 1941.

No. 50

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended Dec. 14.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each Infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1946					1945 (Corresponding Week)				
	(a)	(b)	(c)	(d)	(e)	(a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	31	3	25	—	1	44	2	19	—	1
Deaths		2	—				—	—		
Diphtheria	328	16	87	33	14	575	46	153	79	19
Deaths	3	—	3		—	10	—	2	1	—
Dysentery	68	13	16	4	—	313	44	49	4	—
Deaths					—				—	—
Encephalitis lethargica, acute	—	—	—	—	—	1	—	—	—	—
Deaths		—					—			
Erysipelas			51	9	3			42	17	3
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				36					39	
Deaths	63	7	14		1	42	5	8	19	—
Measles*	6,957	243	318	50	219	619	42	106	167	4
Deaths	6	—	3		1	—	—	—	—	—
Ophthalmia neonatorum	43	3	10	—	—	68	6	15	—	—
Deaths										
Paratyphoid fever	5	1	1 (B)	2 (B)	—	1	—	—	1 (B)	—
Deaths	—	—	—		—	—	—	—	—	—
Pneumonia, influenzal	693	62	12	6	6	969	69	4	4	1
Deaths (from influenza)†	22	2	2		—	69	6	1	1	1
Pneumonia, primary			335	29				205	21	
Deaths		35			7		68		19	6
Polio-encephalitis, acute	—	—				2	—			
Deaths		—					—			
Poliomyelitis, acute	14	—	2	5	1	10	2	1	1	—
Deaths		—					—			
Puerperal fever		3	7		—		4	10		—
Deaths										
Puerperal pyrexia‡	148	8	16	1	—	113	5	10	—	—
Deaths		—					1			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,392	101	332	35	41	1,753	168	307	22	49
Deaths	—	—	—		—	2	—	2	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Typhoid fever	7	1	—	5	1	6	—	6	4	—
Deaths	1	—	—		—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Whooping-cough*	1,664	96	273	57	40	1,195	86	65	42	5
Deaths	7	1	1		—	3	—	—	1	—
Deaths (0–1 year)	495	61	69		13	423	61	49	49	9
Infant mortality rate (per 1,000 live births)										
Deaths (excluding still-births)	5,297	887	649		127	5,775	907	684	218	109
Annual death rate (per 1,000 persons living)			14·3					15·5	14·1	
Live births	9,440	1464	1102		279	6,672	875	824	364	257
Annual rate per 1,000 persons living			22·2					16·5	23·5	
Stillbirths	296	42	39			213	21	33		
Rate per 1,000 total births (including stillborn)			34					39		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

‡ Includes puerperal fever for England and Wales and Eire.

It is still not possible to publish the return of births and deaths for Eire for the weeks ended Oct. 26, Nov. 2, 9, 16, 23, 30, Dec. 7 and 14.

EPIDEMIOLOGICAL NOTES

Neonatal Diarrhoea

The only other outbreak since our report of last week (Dec. 28, p. 1009) is at Stoke-on-Trent.

At the beginning of December the 30-bed maternity unit there had to deal with some 35 cases. During the first week of December two of these mothers complained of diarrhoea, and by the end of the second week nearly a dozen infants were affected. In the infants the onset was explosive, and there have now been four deaths. The four infants were perhaps a week old when the diarrhoea began; in each case the condition terminated fatally after ten or fourteen days. Altogether 10 mothers, 36 infants, and 2 members of the staff appear to have been affected. Bacteriological investigation has not as yet revealed any causative organism. Clearly this outbreak is very like the one at Oxford. It has been of moderate severity, with a case-fatality rate not nearly so high as that in the Leicestershire outbreak.

There have been no further developments in Leicestershire, and at Oxford and Preston the maternity units have now re-opened.

Discussion of Table

In *England and Wales* an increase was recorded in the notifications of measles 491 and scarlet fever 115, and there was a decrease in the incidence of whooping-cough 119.

An increase in the incidence of measles was recorded throughout the country; the largest rises were Kent 119, Yorkshire North Riding 109, and Essex 88. In contrast to the general trend large decreases were recorded for Buckinghamshire 103 and Northumberland 92.

The rise in the notifications of scarlet fever was mainly contributed by the West Midland counties; the largest increase was Warwickshire 30. Small increases in the number of cases of whooping-cough were noted in most counties; the largest variations in the local trends were an increase in Lancashire 41 and a decrease in Yorkshire West Riding 30.

There was an outbreak of diphtheria in Lancashire, Orrell U.D., where the notifications rose from 1 to 29. A fall in the incidence of diphtheria was recorded in London 15 and Durham 10. London had 13 (Chelsea 6) cases of dysentery.

In *Scotland* increases were reported in the notifications of measles 93 and whooping-cough 26, while a decrease was recorded for scarlet fever 28. An increase of 10 in the incidence of diphtheria occurred in the city of Glasgow.

In *Eire* the chief features of the returns were decreases of 23 in cases of diarrhoea and enteritis and of 30 in cases of whooping-cough. The returns for diarrhoea and enteritis were the lowest since the end of August.

In *Northern Ireland* a further increase of 40 was recorded in the outbreak of measles in Belfast C.B.

Quarterly Return for England and Wales

The birth rate during the September quarter was 19.7 per 1,000 and was the highest recorded for any quarter since 1921. Infant mortality was 35 per 1,000 live births and was the lowest rate ever recorded, being 7 below the average for the third quarters of the ten preceding years. The general death rate was 9.3 per 1,000, which was 0.3 above the corresponding quarter of 1945 but 0.5 below the average of the third quarters for 1940–4.

Week Ending December 21

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,201, whooping-cough 1,586, diphtheria 242, measles 7,728, acute pneumonia 741, cerebrospinal fever 29, dysentery 62, acute poliomyelitis 13, paratyphoid 6, typhoid 4.

A Ministry of Health Circular (230/46) to local authorities points out that under the terms of the National Health Service Act the Minister becomes responsible, from the day appointed for its operation, for the provision of hospital and specialist services as defined by section 3 (1) of the Act. In general the Regional Hospital Boards will administer these services, and regulations will be made under section 68 (1) transferring officers employed immediately before the appointed day "solely or mainly at or for the purposes of any hospital transferred to the Minister under the Act (other than teaching hospitals)" to the Boards. The officers referred to include (*a*) those employed at central offices or elsewhere in the authority's hospital service, as well as (*b*) those on the staff of individual hospitals. Authorities are asked to provide particulars, not later than Jan. 31, 1947, of officers in the former class whom they consider likely to be liable to transfer, excluding officers of the mental hospital and mental deficiency services, who will be the subject of a separate inquiry.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Umbilical Swelling

Q.—*A male child was born apparently healthy but separation of the cord was delayed and a fleshy finger of tissue remained protruding from the umbilicus. Now, three months later, all that is visible is a small rounded knob which has a somewhat cystic appearance. The umbilicus, however, weeps continually, and sometimes there is a slight flush around it suggesting inflammation. Is it safe to use silver nitrate to cauterize the umbilicus, or is there any danger of eroding a Meckel's diverticulum and producing a faecal fistula?*

A.—The first point to determine is whether the constant weeping is or is not due to the presence of a fistula. Since there is no faecal discharge there can hardly be any opening of the vitello-intestinal duct, but one must remember that occasionally the opening of a patent urachus may be found at the umbilicus. It is not stated whether the swelling is bright red in colour; if it were so, one might be dealing with the small adenoma which is sometimes found at the umbilicus in young infants. The most likely explanation is that the swelling is a granuloma which ought to develop into fibrous tissue if the parts are kept clean and aseptic. It is unlikely that the application of silver nitrate would do harm, but perhaps the shrivelling up of the tumour might better be obtained by painting with a solution of alum or dilute formalin. If, however, the condition persists, it should be dealt with by a competent surgeon who would make quite sure of the deep relations of the swelling.

Pigmentation in Pregnancy and Lactation

Q.—*A patient of mine had marked pigmentation of the face, particularly over the eyebrows and round the mouth, when she was pregnant. Now that the baby is seven months old (breast-fed) the pigmentation is a little lighter but still persists. Can anything be done about it?*

A.—All authorities agree that there is a tendency to pigmentation during pregnancy. It is suggested that this is due to expansion of the melanophores or pigment-bearing cells of the skin, probably in response to a hormone derived from the posterior pituitary. The most severe and distressing form—chloasma gravidarum—affects the face in the form of yellow or bronze patches. Ballantyne, J. W., and Browne, F. J. (*Trans. Edin. obstet. Soc.*, 1919, **40**, 74), showed that blondes and brunettes are equally liable to this affection, thus disposing of the commonly held idea that such pigmentation occurs mainly in those whose skins are dark.

The pigmentation of the face generally clears up within a few months of confinement. De Lee, J. B. (*Principles and Practice of Obstetrics*, 1940, seventh edition, Philadelphia), states that it tends to disappear when the menses are re-established, but mentions that it may persist for years. This particular patient may therefore expect improvement when lactation is discontinued. No treatment seems to be of any avail, but the judicious use of cosmetics, and possibly of the newer preparations which are supplied in the form of a flat cake applied with a damp sponge, may help to cover the dark patches and thus alleviate the patient's distress.

Menstrual Molimina

Q.—*A woman of 30, with one child of 2 years, has had for the past nine months flooding of thin, almost colourless fluid at her periods. After the third day the loss becomes gradually normal in colour, amount, and consistency. Is there any explanation or treatment for this condition?*

A.—The fluid is probably the natural secretion of the tubes, body of uterus, and cervix—one or all. This secretion is at its maximum in the days preceding the onset of the menstrual flow proper and, to a limited extent, is a normal phenomenon. Thorough examination is indicated to exclude erosion of the cervix, chronic cervicitis, and any lesion causing pelvic congestion. If the findings are negative it is doubtful whether any treatment is necessary apart from simple measures to reduce pelvic congestion. Saline aperients, active physical exercise, and cold baths might help.

It would be interesting to know if this patient shows during the premenstrual phase signs of abnormal fluid retention—increase in weight, oedema, and a sensation of abdominal swelling. If so, it is just possible that the discharge might be part of the general excretion of previously retained fluid which usually occurs at the onset of menstruation in such cases. If this is so, then restriction of the intake of fluid and sodium salts for seven to ten days before menstruation is indicated.

Vitamin A Concentrates

Q.—*How can vitamin A be supplied to a boy showing signs of A deficiency who is allergic to both milk and fish?*

A.—Vitamin A concentrates which do not contain fish oil (e.g., "carotene tabloid," each tablet of which contains 4,500 i.u.) are available. Foods which are good sources of vitamin A, and their contents per 3½ oz. (100 g.) are as follows: spinach, 5,000 i.u.; carrot, 2,000 i.u.; tomato 14 to 16,000 i.u.; cabbage, 960 i.u.; and orange juice 3–400 i.u. Animal livers are also good sources of vitamin A, containing from 2–45,000 i.u. per oz. (30 g.), depending on the type of liver (Hutchinson's *Food and Principles of Dietetics*, 1941, p. 112).

Increase in Tuberculosis

Q.—*What were the notifications of all forms of tuberculosis (pulmonary and non-pulmonary) for the years 1939–45? What is the explanation of the increase, if any?*

A.—The figures for 1945 are not yet available. The notifications for the six years 1939 to 1944 were: 25,355; 26,260; 28,966; 29,560; 30,121; and 30,044. The number of persons not notified before death but dying of tuberculosis during these years were: 2,901; 3,395; 4,383; 3,971; 3,780; and 3,468. The introduction of mass radiography with the consequent earlier discovery of the disease was at first thought to account for the rise, but this suggestion cannot explain the persistent higher incidence and there has undoubtedly been an increase in tuberculosis. This increase is generally attributed to the conditions of life during the war but it is impossible to assess the relative importance of the factors, such as black-out and lack of ventilation, long hours of work, diet, etc., which may have contributed.

Rainbow Haloes

Q.—*A patient aged 65 has been seeing "rainbow" haloes around lights—the red outside, the violet inside—with each eye separately, with both eyes, and with or without glasses. There is no question of glaucoma or cataract. What is the explanation?*

A.—Any structure within the eye which acts as a diffraction grating will produce a rainbow-like halo with the red outside and the blue inside. This may equally be produced by a layer of cells or by droplets of fluid. These two types of halo may be differentiated by passing a stenopeic slit slowly across the pupil. In the former only sectors of the halo diametrically opposed to each other will be seen, which give the appearance of rotating as the slit passes across the pupil. The latter type of halo remains circular and only varies in intensity with the movement of the slit. Haloes may be due to physiological changes in the corneal epithelium and endothelium, lens opacities, and possibly fibrillary intersections of the vitreous; or to mucus, blood, pus, or small air bubbles in the lacrimal secretion, or other material on the surface of the cornea; or also to oedema of the deeper layers of the corneal epithelium due to glaucoma or photophthalmia from exposure to ultra-violet light.

The diameters of haloes vary, and when measured from the point of origin of the causal incident light the yellow ring of a lenticular halo subtends 6° to 7°. The ring due to material on the surface of the cornea is large—up to 14°—and of course disappears when the cornea is cleaned. A halo without differentiation in colour is common in normal eyes under ideal conditions.

Treatment of Syphilis

Q.—*The wife of a G.P.I. has a strongly positive Wassermann reaction but no clinical signs of syphilitic infection. How should she be treated?*

A.—With the somewhat meagre details available this question is difficult to answer. We should like to know the age of the patient and her obstetrical history, whether she is past the child-bearing age, and whether there have been any miscarriages. Assuming that the patient is syphilitic but has no cardiovascular lesion and has passed the menopause, everything depends on the state of her cerebrospinal fluid. If this is completely negative (Wassermann, cells, protein, and colloidal gold reaction) it seems doubtful if any treatment is necessary. As an insurance one or two courses of bismuth each year for a few years might be worth while, each course to consist of ten weekly injections of 0.25 g. of an insoluble salt. On the other hand if the fluid is positive, and more particularly if the pathological changes are well marked, active treatment is indicated without delay. This should consist of penicillin and fever therapy—preferably artificially induced malaria. At least 4 million units of penicillin should be given by intramuscular injection, either in doses of 40,000 units three-hourly or in doses of 300,000 units twice daily; the malaria should be induced by injection of infected blood and about twelve paroxysms allowed before it is terminated. The follow-up should include examination of the cerebrospinal fluid every six months.

Chemotherapy and Appendicitis

Q.—*Now that we have unlimited penicillin and a large range of sulphonamides, what is considered the best treatment for acute perforated appendicitis and general peritonitis? Should penicillin be given, and which sulphonamide is advised in what dosage (assuming operation has been carried out)?*

A.—The answer to this question is implicit in the bracketed phrase at the end of the paragraph. The treatment of acute perforated appendicitis and general peritonitis is still the operation of appendicectomy, followed by nasal suction drainage of the upper alimentary tract and adequate fluid and salt replacement by the intravenous route. Penicillin and sulphonamides have added to this management only in slight degree. The systematic administration of penicillin will prevent certain of the pulmonary complications of peritonitis and will control any septicaemic manifestations. This is true even when the dominant peritoneal organism is penicillin-resistant, for the metastatic lesions in the chest may well be due to a secondary and penicillin-sensitive infection. Penicillin given systematically does not appear in great concentration in the peritoneal cavity, and if given locally it will be inactivated by the penicillin-resistant coliform organisms which complicate peritonitis in its later stages. The soluble sulphonamides may be given by way of the intravenous drip; it has not been clearly shown that the local application of sulphonamides to the peritoneum at the time of operation reduces the mortality significantly. *Str. faecalis* is highly resistant to penicillin, and for bacterial stasis of this organism the concentration of penicillin required is difficult to obtain in the peritoneal cavity.

Ultraviolet Irradiation Without Goggles

Q.—*Can a carbon arc sunlight lamp be used with safety at say 2 ft. (60 cm.) from the face, for five to ten minutes on alternate days, without protective goggles, provided the eyelids are kept closed?*

A.—If the "carbon arc sunlight lamp" in question does not produce more than a first-degree reaction on the face under the stated conditions, there is no need to wear goggles provided the eyes are kept shut. There always exists the possibility of producing—with the same dosage—a second-degree reaction of the more delicate skin of the eyelids. The resulting discomfort and oedema of the loose tissues are easily avoided by smearing the eyelids with cold cream or zinc oxide ointment before irradiation.

Incidentally, it is more effective and more aesthetic to treat the face in two halves with the lamp not directly in front of the patient but over to one side. This can be achieved by making the patient face the lamp and then turn the head through 45° one way, then the other, for the same exposure.

Letters and Notes

Panophthalmitis After Cataract Operations

Dr. J. T. MACLACHLAN (Glasgow) writes: I am of opinion that if Lister's antiseptic technique is employed in operations on the eye, panophthalmitis and other complications would not arise. Dr. William MacKenzie, the famous Glasgow oculist, devised over 100 years ago an excellent antiseptic lotion for diseases of the eye. MacKenzie's lotion consists of: bichloride of mercury 1 gr. (65 mg.), chloride of ammonium 6 gr. (400 mg.), coccus cacti (cochineal) 1½ gr. (100 mg.), Aq. 6 oz. (170 ml.). Of this lotion a little—about a spoonful—is diluted with equal parts of warm water, and the eye bathed several times daily with a piece of linen or sponge, and the head titlted back and some of the lotion allowed to run into the eye. If MacKenzie's lotion were used several times daily for one week before operation and for some time after the operation, I believe septic complications would not arise. To prevent haemorrhage in the eye after operations for cataract, if the blood pressure is high it can be safely reduced to 120 by giving "liq. trinitrini" 1 or 2 min. (0.06 or 0.12 ml.) along with some spirits of sweet nitre some time before and after the operation.

Definition of Health

Mr. PATRICK SLATER writes: The *Oxford English Dictionary* authorizes the use of the word "health" to indicate a variable state. I have never known anyone take etymological exception to the question. "How is your health?" or to qualifying "health" with such adjectives as excellent, good, indifferent, or poor. Indeed, until some qualifying words are added, an individual's health remains undefined. Moreover the World Health Organization, the Ministry of Health, the United States Public Health Service, etc., do not limit their terms of reference to states of complete physical, mental, and social well-being. If as a result of the decision of the World Health Organization the word "health" is henceforth to be applied only to such a state, may I ask: Has the word any connotation whatever? What comprehensive term, if any, applies universally to all the observable conditions which approximate to or deviate from this perfect state? How can their decision be enforced?

Notes from Russia

Dr. W. P. FORREST, chief medical officer of the U.N.R.R.A. Mission to the Soviet Ukraine, sends us the following medical news from Kiev: The late Prof. Alexander Bogomoletz, whose work on the antireticular cytoxic serum was outlined in this *Journal* (1943, **2**, 203), has been succeeded as President of the Ukrainian Academy of Sciences by Alexander B. Palladin, a member of the Ukrainian, Byelorussian, and U.S.S.R. Academies of Sciences and of the All Union Academy of Medical Sciences. Palladin has written over 150 scientific papers, and has founded many institutes and societies. His latest work is on vitamins and the biochemistry of muscular action. The son of Prof. Bogomoletz is now director of the famous Kiev Institute of Pathological Physiology. Academician V. P. Filatov is once more installed in the partially reconstructed Filatov Ophthalmological Institute. He has arranged to do several articles in English on tissue therapy in ophthalmology and leprosy. There is an enormous demand here for literature to replace the medical libraries, which were almost completely destroyed by the invaders. Not only are old journals and books required to replace those lost, but recent and current books and journals are more than welcome. They can be sent c/o the U.N.R.R.A. Mission to the Ukraine, or to I. F. Kononenko, People's Minister of Health, Kiev, Ukrainian S.S.R.

Corrections

In the article headed "Classifying Causes of Death" (*Journal*, Dec. 21, 1946, p. 957) the chairman of the Medical Advisory Committee, Sir Ernest Rock Carling, should have been described as *formerly* Dean of Westminster Hospital Medical School.

A misprint occurred in the article by Dr. A. J. Suchecki on "Allergic Reactions to Penicillin" (*Journal*, Dec. 21, 1946, p. 938). Under the subheading "Review of the Literature" the word "included," in the second line from the end, should read "excluded."

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